EXPERT REPORT, ANNA LEMBKE, M.D.

March 25, 2019

MDL No. 2804

Relating to Case Nos. 17-OP-45004 and 18-OP-45090

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A. Background and Qualification

1. I am an Associate Professor, Chief of the Addiction Medicine Dual Diagnosis Clinic, Medical Director of Addiction Medicine, and Program Director of the Addiction Medicine Fellowship, in the Department of Psychiatry and Behavioral Sciences at Stanford University School of Medicine. Since 2016, I also hold a Courtesy Appointment in the Stanford University Department of Anesthesiology and Pain Medicine. I began my faculty career at Stanford in 2003. A true copy of my current CV is attached to this Report as Exhibit A.

2. I received my undergraduate degree in Humanities from Yale University in 1989, and my medical degree from Stanford University in 1995, where I also completed a partial residency in Pathology (1997) and a full residency in Psychiatry (2000), as well as a Fellowship in Mood Disorders, Department of Psychiatry and Behavioral Sciences (2002).

3. I have been licensed to practice medicine in the State of California from 1995 to the present. I received the DEA-X waiver to prescribe buprenorphine products in 2013. I am a diplomate of the American Board of Psychiatry and Neurology (2003; recertified, 2013), and a diplomate of the American Board of Addiction Medicine (2013).

4. From 2001 to the present, I have taught medical students, residents, and fellows at Stanford University School of Medicine, on a diversity of topics related to psychiatry, addiction, and pain. For example, from 2004 to the present, I have given annual lectures on addiction medicine within the Practice of Medicine (POM) series for Stanford medical students, including topics such as the neurobiology of addiction, how doctors should intervene when they detect substance use problems, and how to have difficult conversations with patients on the topic of substance use, misuse, overuse, and addiction.

5. I received the Stanford Award for Excellence in Academic Teaching, Department of Psychiatry, in 2014, and again in 2018.

6. As a full time faculty at the Stanford University School of Medicine, I regularly treat patients with addiction to opioids and other substances. For the last 15 years, my clinical practice has included a significant proportion of patients taking prescription opioids for pain relief, for whom such drugs have resulted in misuse, dependence, and addiction. As an integral part of my practice, I work with these patients to develop treatment plans that will address their pain while making appropriate efforts to reduce (taper) or eliminate use of opioids, and/or treat their opioid addiction. Such plans can include non-opioid medications for pain, as well as alternative, non-pharmaceutical modalities, and counseling, with a dual focus on treating the underlying painful condition and the substance use disorder. I also see patients within the Stanford Pain Clinic, where I provide expert consultation in pain and addiction.

7. In 2015, I received the Stanford Chairman's Award for Clinical Innovation for developing inpatient and outpatient clinical services dedicated to helping people with substance use problems.

8. In January 2015 I was appointed by Governor Jerry Brown to the Research Advisory Panel of California. I served on the Panel until 2017. I, along with the other Panel members, was tasked with assessing the safety of clinical trials to be conducted in the state of

California using controlled substances, such as opioids. In this capacity, I applied my knowledge and experience to the review of study designs and protocols, and I made recommendations for procedures to protect patients in these trials, including, in particular, protection from potential harmful effects of opioids.

9. Since 2015 I have served on the Board of the California Society of Addiction Medicine (CSAM). I have been a member of CSAM, and the American Society of Addiction Medicine (ASAM), since 2011.

10. In 2016 I chaired the Planning Committee for the California Society of Addiction Medicine (CSAM) Annual Addiction Medicine Conference.

11. In 2016, I became president of the Addiction Medicine Fellowship Directors Association (AMFDA).

12. In 2016 I led a program funded by the Stanford Center for Continuing Medical Education (SCCME), titled, "Tapering Patients off of Chronic Opioid Therapy."[1]

13. Since 2016, I have chaired the Addiction Medicine Task Force, Stanford University School of Medicine. The goal of the Task Force is to re-evaluate and re-create the medical school curriculum on addiction and safe prescribing of addictive substances. I have served as MedScholar Advisor on the topic of *Developing the Addiction Curriculum at Stanford*, Stanford University School of Medicine.

14. I am the author of a book on the prescription drug epidemic: "Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop" (Johns Hopkins University Press, October 2016).[2]

15. I have published over 50 peer-reviewed articles, chapters, and commentaries, which have appeared in the New England Journal of Medicine, Journal of the American Medical Association, Pain Medicine, Journal of General Internal Medicine, Addiction, and other peer reviewed journals. Many of these publications address the diagnosis and treatment of addiction, as well as the treatment of pain. I have also published articles on the importance of teaching addiction medicine in medical school, residency, and fellowship, (as discussed in this report).

16. In 2016 I co-authored a peer-reviewed article, "Weighing the Risks and Benefits of Chronic Opioid Therapy," American Family Physician 2016; 93:982-990, which addressed issues of opioid misuse and addiction, risk assessment and mitigation, patient education, tapering to reduce or end opioid exposure, tolerance, dependence, and risks of overdose.[3] American Family Physician is among the most read family physician peer reviewed journals. The readership includes 32,000 medical students and over 3,700 nurse practitioner and physician assistant subscribers.

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[1] https://med.stanford.edu/cme/courses/online/opioid-taper.html

[2] Lembke A. *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*. 1st ed. Johns Hopkins University Press; 2016

[3] Lembke A, Humphreys K, Newmark J. Weighing the risks and benefits of chronic opioid therapy. *Am Fam Physician*. 2016; in press

17. In 2016 I co-authored a Research Letter, JAMA Intern Medicine 2016;176(2):259-261, which examined Medicare data on opioid drug prescription patterns. Our analysis concluded that opioid prescribing is "a widespread practice relatively indifferent to individual physicians, specialty or region. High-volume prescribers are not alone responsible for the high national volume of opioid prescriptions. Efforts to curtail national opioid overprescribing must address a broad swath of prescribers to be effective." [4](pp. 260-261) This article has been cited 71 times in the 3 years since its publication, and has helped to counter the notion that the epidemic of opioid drug misuse and addiction is primarily attributable to a small group of "pill mill" doctors.

18. In 2016 I co-authored a Research Letter, JAMA Psychiatry, 2016;73(9), on the high exposure to opioids among Medicare patients, the growing incidence of opioid use disorder in this population, and the lack of buprenorphine prescribers in this population, noting the gap between the need for treatment, and access to that treatment.[5]

19. In 2018 I co-authored two articles in peer-reviewed pain journals on pain management of patients with chronic pain and opioid use disorder.[6,7]

20. I have testified before the United States House of Representatives on the opioid epidemic and possible means to mitigate harms caused by that epidemic, and I have presented at numerous conferences before governmental, professional, academic and lay audiences on related topics.

21. In forming the opinions expressed in this Report, I have relied on my medical training, more than twenty years of clinical experience, and my own research on opioid prescribing. My research began circa 2001 and has been multimodal. I have done qualitative interviews with patients, providers, and others in the health care field on questions related to opioid prescribing. I have followed and analyzed the medical literature using PubMed and other academic search engines, along with different combinations of key words such as "pain, opioids, treatment, randomized clinical trials, open label trials, effectiveness, adverse effects, prescribing, addiction, dependence, overdose, etc. …" I have compiled statistics published by the CDC and other government agencies. I have, in collaboration with colleagues, analyzed opioid prescribing databases such as Medicare Part D.[8,9] As a regular and ongoing part of my practice, I conduct literature searches of research on the subjects of addiction and pain treatment, which is essential

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[4] Chen JH, Humphreys K, Shah NH, Lembke A. Distribution of opioids by different types of medicare prescribers. *JAMA Intern Med*. December 2015:1-3. http://dx.doi.org/10.1001/jamainternmed.2015.6662, at pp. 260-261.

[5] Lembke A, Chen JH. Use of opioid agonist therapy for medicare patients in 2013. *JAMA Psychiatry*. 2016;73(9). doi:10.1001/jamapsychiatry.2016.1390

[6] Harrison TK, Kornfeld H, Aggarwal AK, Lembke A. Perioperative Considerations for the Patient with Opioid Use Disorder on Buprenorphine, Methadone, or Naltrexone Maintenance Therapy. *Anesthesiol Clin*. 2018;36(3):345-359. doi:10.1016/j.anclin.2018.04.002

[7] Lembke A, Ottestad E, Schmiesing C. Patients Maintained on Buprenorphine for Opioid Use Disorder Should Continue Buprenorphine Through the Perioperative Period. *Pain Med*. 2018;(February):1-4. doi:10.1093/pm/pny019

[8] Chen et.al, "Distribution of Opioids," fn. 4, above, at p. 259

[9] Lembke, *et al.*, "Use of Opioid Agonist Therapy," fn. 5, above, at p. 990

to my work with my patients. Indeed, given the large and increasing role of opioid drugs in addiction, the fields of addiction and pain medicine are inevitably intertwined, such that it is essential to my practice to remain aware of the state of scientific inquiry in both fields. Specifically for this Report, I have considered the materials listed on Exhibit B, attached. I hold the opinions stated in this Report to a reasonable degree of scientific certainty.

22. A statement of my testimony within the last 4 years is attached as Exhibit C and a statement of my compensation rate for consulting work is attached as Exhibit D.

B. Opinions

For the reasons set forth in detail in this Report, I hold the following opinions:

1. Addiction is a chronic, relapsing and remitting disease with a behavioral component, characterized by neuroadaptive brain changes resulting from exposure to addictive drugs. Every human being has the potential to become addicted. Some are more vulnerable than others. Risks for becoming addicted include genetic, developmental, and environmental factors (nature, nurture, and neighborhood). One of the biggest risk factors for addiction is simple access to addictive drugs. Prescription opioids are as addictive as heroin, and the Defendants' conduct in promoting widespread access to prescription opioids has inevitably resulted in an epidemic of opioid addiction.

2. Opioid prescribing began to increase in the 1980's, and became prolific in the 1990's and the early part of the 21st century, creating more access to opioids across the U.S. population, and representing a radical paradigm shift in the treatment of pain. Prior to 1980, doctors prescribed opioid pain relievers sparingly, out of appropriate concern that their patients would get addicted, and then only for short term use in cases of severe injury, surgery, or at the very end of life.

3. The Pharmaceutical Opioid Industry increased sales of prescription opioids, by directly targeting doctors, by promoting key opinion leaders, by infiltrating continuing medical education courses, by supporting professional medical societies, and by co-opting medical watchdog organizations like The Joint Commission, to convince prescribers that liberal opioid prescribing is based on science. In fact there has never been sufficient evidence to justify widespread opioid prescribing.

4. The Pharmaceutical Opioid Industry encouraged and promoted several misconceptions concerning opioid use, including the following:

   a. overstatement of benefits of long-term use for chronic pain. In fact, there is not, and has never been, reliable evidence that long-term opioid use improves pain or function to any clinically meaningful degree. The best evidence available shows that there is little or no improvement in pain or function for most patients on long-term opioid therapy. Patients often endorse ongoing subjective benefit from the opioid, not because it is treating underlying pain, but because it is relieving opioid withdrawal from the previous dose. Studies show that pain improves when patients on chronic high dose opioid therapy reduce their dose or come off opioids.

Limiting opioid prescribing is good medicine, because it decreases exposure to a dangerous and potentially lethal drug, without compromising pain treatment. As a part of the overstatement of benefits, the Pharmaceutical Opioid Industry promoted the concept of "undertreatment of chronic pain" on a massive scale. The number of people who suffer from chronic pain varies substantially, depending on how "chronic pain" is defined. Regardless of the definition or true number, the fact remains that there is insufficient evidence that long-term opioid therapy effectively treats chronic pain.

b. making inaccurate understatements of the risks of addiction to opioids. Even when being prescribed by a doctor for a legitimate pain condition, opioid painkillers are as addictive as heroin purchased on a street corner, because the prescription opioids have the same addictive effects on the neurocircuitry of the brain. There is not, and has never been, scientific support for the claim that the risk of addiction from chronic opioid therapy is low, "rare," or "less than 1%." In fact, the best evidence available shows that the risk of addiction in patients taking opioids for chronic pain is between 10% and 29%. In teens and young adults, the evidence shows that even very limited exposure to prescription opioids can result in addiction. So-called "abuse-deterrent formulations" do not lower the risk of addiction among patients taking them as prescribed.

c. making inaccurate claims as to the levels to which doses can be safely increased. With increasing dosage and duration of opioids, the risk of addiction goes up, as do the risks of many other adverse health consequences, including tolerance, dependence, withdrawal, opioid induced hyperalgesia, immunosuppression, severe constipation, depression, cognitive decline, cardiac effects, breathing effects, hormonal effects, accidental overdose, and death. There is an undeniable link between opioids and suicides. Opioids are associated with more adverse medical outcomes and more mortality than non-opioid analgesics (NSAIDS).

d. mischaracterizing addictive behavior as "pseudoaddiction" and tolerance as "breakthrough pain." There is no such thing as "pseudoaddiction," and no evidence that providing more opioids is an appropriate response to patients exhibiting drug-seeking behavior. On the contrary, tolerance, dependence, and withdrawal, markers of neuroadaptation to the drug, constitute an adverse medical reaction and should trigger consideration of tapering the opioid medication, not increasing its dose.

e. characterizing opioid dependence as a benign state that is easily reversible. Prescription opioids induce physiological dependence almost universally, and dependence leads to addiction in a significant subset of users, particularly as dose and duration of exposure are increased. Once established, opioid dependence represents a complex, debilitating, and

sometime irreversible clinical problem. In most cases, these patients require a protracted, medically supervised taper to lower their doses. In some cases, the suffering from withdrawal is so extreme that patients say they would rather die than go through it. Indeed, people can die from opioid withdrawal, due to vital sign instability, suicide, and other complications.

f. inaccurate claims as to the validity of patient screening as a predictor of who will become addicted. The largest risk factors for addiction are dose and duration of opioid exposure, regardless of whether a particular patient may have identifiable risk factors in his or her social or genetic history. It is difficult, if not impossible, to predict in advance who will and will not get addicted to a prescription opioid. When it occurs in patients taking opioid medications for pain, addiction is neither easy to identify nor easily managed.

5. In sum, the Pharmaceutical Opioid Industry made misleading marketing claims to promote the above misconceptions, in the absence of reliable scientific evidence. Taken together, these misconceptions were a primary driver of the massive increase in the sale of opioids and the resulting epidemic of dependence and addiction, as detailed in this Report. Further, the actions of the Pharmaceutical Opioid Industry significantly influenced doctors and others who made decisions that increased the population's exposure to prescription opioids. Other developed countries with similar populations that experience chronic pain, but which have not had the same aggressive marketing as in the U.S., have not experienced any comparable degrees of prescription opioid overuse, mortality, and morbidity.

6. The increase in opioid sales resulted in a prescription opioid epidemic in the United States. "Epidemic," defined as an outbreak of disease that spreads quickly and affects many individuals at the same time, is the appropriate term to describe the increase in opioid related morbidity and mortality beginning in the 1990's and continuing to the present day. This epidemic is first and foremost a prescription opioid epidemic, with prescription opioids accounting for a higher number of cumulative deaths to date (1999-2017) than heroin and illicit fentanyl combined.

7. We are now in the second and third waves of this epidemic, with a spike in deaths from illicit opioids, particularly heroin (second wave) and illicit fentanyl (third wave). There is a clear link between prescription opioid exposure and the subsequent use of heroin and other illicit opioids. The likelihood of heroin addiction is 40 times greater in those who have previously misused or been addicted to prescription opioids.

8. The increased sales of prescription opioids harmed communities by causing individuals who otherwise would not have been exposed to opioids, to be exposed and become addicted, including individuals who turned from prescription opioids to illicit sources of opioids such as heroin (The Gateway Effect).

9. The increased sales of prescription opioids harmed communities by causing individuals who otherwise would not have been exposed to opioids, to become dependent on

opioids (independent of addiction), and suffer significant morbidity and mortality as a result (The Dependence Effect).

10. The increased sales of prescription opioids harmed communities by causing a dramatic increase in the widespread availability of opioids, including to persons for whom opioids had not been prescribed (The Tsunami Effect). Medical prescriptions are the primary conduit for prescription opioid misuse. Less than 10% of Americans misusing prescription opioids got them from a "street dealer."

11. Others bear some lesser responsibility for the events that have transpired since 1995 with respect to the overuse of prescription opioids. However, none of those events would have occurred, nor would they have been possible, but for the aggressive marketing by the Pharmaceutical Opioid Industry and the myths of significant benefits versus low risk that they promoted, as outlined above and detailed in the body of this Report.

12. Ending the epidemic of opioid addiction, dependence, and death will require significant investment of resources. An effective strategy will be multifaceted, and will accomplish the following: prevent new cases of addiction, dependence, and other related harms (primary prevention), limit progression of harm (secondary prevention), and treat existing cases (treatment). These changes will require curbing opioid prescribing, re-educating patients and health care providers, creating de-prescribing clinics, promoting naloxone and other harm-reduction strategies, and building an enduring medical infrastructure to treat addiction.

C. Detailed Statement of Opinions

1. Addiction is a chronic, relapsing and remitting disease with a behavioral component, characterized by neuroadaptive brain changes resulting from exposure to addictive drugs. Every human being has the potential to become addicted. As stated by the CDC, "Anyone who takes prescription opioids can become addicted to them."[10] Some are more vulnerable than others. Risks for becoming addicted include genetic, developmental, and environmental factors (nature, nurture, and neighborhood). One of the biggest risk factors for addiction is simple access to addictive drugs. Prescription opioids are as addictive as heroin, and the Defendants' conduct in promoting widespread access to prescription opioids has inevitably resulted in an epidemic of opioid addiction.

a. Addiction is the continued use of a substance despite harm to self and others and/or a desire to quit or cut back. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[11] uses the term "substance use disorder" to denote addiction. I use the terms "opioid addiction" and "opioid use disorder" interchangeably here.

b. DSM-5 denotes 11 different criteria to diagnose an opioid use disorder (OUD) (p. 541). A short-hand way to remember these criteria is the "four

[10] https://www.cdc.gov/drugoverdose/opioids/prescribed.html.

[11] *Diagnostic and Statistical Manual of Mental Disorders*. Washington, DC: American Psychiatric Association (DSM-5); 2013

C's": Control, Compulsion, Craving, and continued use despite Consequences.

i. Control refers to out-of-control use, for example using more than intended, or an inability to cut back use when necessary.

ii. Compulsion refers to mental preoccupation with using against a conscious desire to abstain.

iii. Craving refers to physiologic and/or mental states of wanting.

iv. Consequences refers to the social, legal, economic, interpersonal, and other problems that arise as a result of use, yet which still do not deter use.

c. The physiological phenomena of tolerance and withdrawal are included in the DSM-5 criteria, but they are not required in order to make the diagnosis of opioid use disorder/addiction. In other words, tolerance, dependence, and withdrawal are recognized as separate physiologic phenomena often seen in addiction, but not definitional for addiction. The DSM-5 also recognizes that addiction is a spectrum disorder, divided into mild, moderate, and severe, based on the number of criteria met.[12]

d. The American Society of Addiction Medicine (ASAM) has defined addiction as follows: "Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors. Addiction is characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death."[13] This ASAM definition of addiction is consistent with but not identical to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). The ASAM definition does not single out any specific substance, highlighting the idea that all addictive drugs work on the same common brain pathway.

[12] DSM-5, fn. 11, above, pp. 541-542.
[13] American Society of Addiction Medicine (ASAM) Definition of Addiction. https://www.asam.org/resources/definition-of-addiction; accessed June 20, 2018, at p. 1.

e. From a neuroscience perspective, addiction is a disorder of the brain's reward circuitry.[14] Opioids, in addition to binding the mu-pain receptors, also cause the release of the neurotransmitter dopamine. In order to accommodate the high amount of dopamine released, the brain adapts by downregulating its own endogenous dopamine and its own endogenous dopamine receptors. This process is called neuroadaptation, and the result is a dopamine deficit state, wherein the threshold for experiencing pleasure goes up, and the threshold for experiencing pain goes down. Addicted individuals then need the substance not to feel good, but to escape the pain of withdrawal.

f. In severe forms of addiction, individuals commit all available resources to obtaining more of the substance, even forgoing natural rewards like food, finding a mate, or raising children.[15] By hijacking the brain's reward and motivational centers, addiction leads to compulsive, self-destructive consumption that overcomes the limits of voluntary choice.

g. Because addiction affects the same neural pathways evolved over millions of years to encourage humans to seek out pleasure and avoid pain, everyone is vulnerable to the disease of addiction. Or as Nora Volkow, Director of the National Institute on Drug Abuse, and Thomas McLellan, former Deputy Director of the Office of National Drug Control Policy, wrote in their review "Opioid Abuse in Chronic Pain" in the New England Journal of Medicine (2016), "no patient is immune to addiction."[16] Without activation by consumption of the drug, the disease of addiction does not exist. This is supported by studies that have identified a dopamine receptor deficit state among those exposed to addictive drugs, compared to healthy subjects who have not been exposed.[17] Exposure to/consumption of the addictive substance is a necessary criterion for the development of addiction to that substance.

2. Opioid prescribing began to increase in the 1980's, and became prolific in the 1990's and the early part of the 21st century, creating more access to opioids across the U.S. population, and representing a radical paradigm shift in the treatment of pain. Prior to 1980, doctors prescribed opioid pain relievers sparingly, out of appropriate concern that their patients would get addicted, and then only for short term use in cases of severe injury, surgery, or at the very end of life.

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[14] Koob GF, Volkow ND. Neurocircuitry of addiction. *Neuropsychopharmacology*. 2010;35:217-238. doi:10.1038/npp.2010.4

[15] Schultz W. Potential vulnerabilities of neuronal reward, risk, and decision mechanisms to addictive drugs. *Neuron*. 2011;69(4):603-617. doi:10.1016/j.neuron.2011.02.014

[16] Volkow ND, McLellan AT. Opioid Abuse in Chronic Pain - Misconceptions and Mitigation Strategies. *N Engl J Med*. 2016;374(13):1253-1263. doi:10.1056/NEJMra1507771, at p. 1254.

[17] Koob *et.al*, "Neurocircuitry," fn. 14, above, p. 223; Volkow ND, Fowler JS, Wang G-J, Swanson JM. Dopamine in drug abuse and addiction: results from imaging studies and treatment implications. *Mol Psychiatry*. 2004;9(6):557-569. doi:10.1038/sj.mp.4001507 at p. 557

a. Prior to 1980, doctors used opioid pain relievers sparingly, and only for the short term in cases of severe injury or illness, during surgery, or at the very end of life. [18] Doctors' reluctance to prescribe opioids stemmed from the legitimate concern that patients would get addicted.

i. Awareness of the risks of addiction caused by opioids ingested in the context of medical care, dated back at least to the Civil War, when injured soldiers became addicted to morphine, and heroin was available over the counter next to Bayer aspirin as a cough and cold remedy, leading to the opioid epidemic of the early 1900s. [19](

ii. A study published in 1954 reported that 27% of opioid addicted white males (137/508) and 1.2% of African American males (4/330) yielding a combined rate of 16.8% (141/838), became addicted after being treated with opioids for pain. The authors successfully tapered these patients off of opioids, with improved pain and function in more than 80%. The authors concluded, "Morphine is not the answer to chronic pain. Because of the development of tolerance to the analgesic effects of morphine, alleviation of pain becomes inadequate. Under such circumstances the physician, by gradually withdrawing narcotics, does not deprive the patient of any actual benefit but protects him and his family from the possible legal, social, or economic difficulties attendant on opiate addiction. The administration of morphine to a patient with chronic pain is a short-lived type of kindness. Long-term kindness would begin when opiates are withheld or withdrawn in favor of other therapeutic measures."[20]

iii. This history contributed to the longstanding reluctance of the medical profession to prescribe opioids prior to the marketing campaigns carried out by the Defendants as described below.

b. Opioid prescribing tripled between the 1990's and 2012, and dramatically increased in dose and duration. "By 2010, enough OPR [opioid pain relievers] were sold to medicate every American adult with a typical dose of 5 mg of hydrocodone every 4 hours for 1 month." [21]

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[18] Meldrum ML. *Opioids and Pain Relief: A Historical Perspective (Progress in Pain Research and Management, V. 25)*. IASP Press; 2003, at pp. 195-199.
[19] Courtwright DT. *Dark Paradise: A History of Opiate Addiction in America*. Harvard University Press; 2001, at pp. 45-46; 89-91.
[20] Rayport M. Experience in the Management of Patients Medically Addicted to Narcotics. *JAMA - J Am Med Assoc*. 1954;156(7):684-691, at p. 690.
[21] Paulozzi LJ, Jones CM, Mack K a, Rudd R a. Vital Signs: Overdoses of Prescription Opioid Pain Relievers --- {United States}, 1999–2008. *MMWR Morb Mortal Wkly Rep*. 2011;60(43):1487-1492, http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6043a4.htm?s_cid=mm6043a4_w, at p. 1489.

i. From 1996 to 2011 there was a 1,448% increase in the medical use of opioids, with increases of 690% from 1995 to 2004 and 100% from 2004 to 2011. Over the same time period, opioid misuse increased more dramatically: 4,680% from 1996 to 2011, with increases of 1,372% from 1996 through 2004 and 245% from 2004 to 2011. The number of patients seeking treatment for opioid use disorder in this time period, not including heroin, increased 187%, whereas treatment-seeking increased 87% for heroin, 40% for marijuana, and decreased 7% for cocaine. [22] The increase in the medical use of opioid analgesics during this time period contributed to increases in misuse and addictive use.

ii. "By 2005, long-term opioid therapy was being prescribed to an estimated 10 million US adults. The volume of prescribed opioid analgesics was 100 MME per person in 1997; in 2007, the MME per person had increased to almost 700 MME."[23] (A very recent study found that the 2017 level of MME had declined from its peak to 543.4 MME, which remains well over 5 times higher than the prescribing rate in 1997.[21]

iii. The number of long-term opioid users (daily for greater than 90 days) increased between 1999 and 2014. "Of all opioid users in 2013-2014, 79.4% were long-term users compared with 45.1% in 1999-2000."[24] The increase in long-term use is important, because increased duration of use is also directly correlated with risk of addiction.[25]

iv. Between 2006 and 2015, 66% of patients receiving an opioid prescription in an ambulatory (outpatient) care setting had a diagnosis of non-cancer pain, and 28% had no pain diagnosis at all. Only 5% of patients had a cancer-related pain diagnosis. Absence of a pain diagnosis was more common in visits where an opioid

[22] Atluri S, Sudarshan G, Manchikanti L. Assessment of the trends in medical use and misuse of opioid analgesics from 2004 to 2011. *Pain Physician*. 2014, at p. E119.

[23] Paulozzi LJ, Weisler RH, Patkar A a. A national epidemic of unintentional prescription opioid overdose deaths: how physicians can help control it. *J Clin Psychiatry*. 2011;72(5):589-592. doi:10.4088/JCP.10com06560, at p. 589; *for 2017 figures, see* Schieber LZ, Guy, GP, Seth P, *et al.* Trends and Patters of Geographic Variation in Opioid Prescribing Practices by State, United States, 2006-2017. JAMA Netw Open. 2019;2(3):e190665, at p. 1.

[24] Mojtabai R. National trends in long-term use of prescription opioids. *Pharmacoepidemiol Drug Saf*. 2017. doi:10.1002/pds.4278, at p. 526.

[25] Edlund MJ, Martin BC, Russo JE, Devries A, Braden JB, Sullivan MD. The Role of Opioid Prescription in Incident Opioid Abuse and Dependence Among Individuals With Chronic Noncancer Pain. *Clin J Pain*. 2014;30(7):557-564, at p. 557.

prescription was continued (30.5%) than those in which an opioid was newly prescribed (22.7%).[26]

v. As reported in an article I co-authored in 2016, more than one-third of Part D Medicare enrollees fill at least one opioid prescription in any given year. Part D covers 68% of the roughly 55 million people on Medicare.[27] As such, more than 10 million Part D Medicare enrollees are exposed to a prescription opioid in any given year, thus becoming vulnerable to the adverse effects of opioids, including but not limited to addiction. Medicare represents just one patient population, suggesting that many millions of patient consumers in this country have been exposed to the risks of prescription opioids in recent decades, both within and outside the Medicare-eligible populations. As discussed later in this report, much of that exposure resulted from aggressive marketing that overstated benefits and downplayed risks of chronic exposure to prescription opioids.

c. As reported in another article I co-authored in 2016, increased opioid prescribing is distributed across different types of prescribers, relatively indifferent to individual physicians, specialty or region.[28] In other words, opioid overprescribing is not the result of a small subset of so-called 'pill mill' doctors, although such doctors do exist, but rather has been driven by a wholesale shift in medical practice. All doctors across diverse medical specialties are prescribing more opioids.

i. By specialty, pain doctors prescribe more opioids than doctors in any other specialties. However, by volume, family medicine and internal medicine doctors account for the most opioids, simply because there are more of them.[29]

ii. But the salient finding was that opioid prescribing is not driven by a minority of prolific prescribers.[30]

d. Although national average opioid prescribing has plateaued or decreased since its peak in 2012, there are still many cities, counties, and states across the nation where opioid prescribing continues to be high, and overall opioid prescribing in the US remains at levels far exceeding pre-1990 rates.

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[26] Sherry TB, Sabety A, Maestas N. Documented Pain Diagnoses in Adults Prescribed Opioids: Results From the National Ambulatory Medical Care Survey, 2006–2015. *Ann Intern Med*. 2018;169(12):892-894, at p. 892.
[27] Lembke *et al.*, "Use of Opioid Agonist Therapy", fn. 5, above, at pp. 990-991.
[28] Chen et.al, "Distribution of Opioids", fn 4, above, at p. E2.
[29] *Id.* at pp. E1-E2.
[30] *Id.* at p. E2.

i. The U.S. national average number of opioid prescriptions written in 2012 was 81 opioid prescriptions per 100 persons (255 million total prescriptions). By 2016, the U.S. national average had decreased to 66 opioid prescriptions per 100 persons (214 million total). In 2017, the prescribing rate had fallen to its lowest in more than 10 years, at 59 prescriptions per 100 persons (total of more than 191 million total opioid prescriptions).[31]

ii. However, prescribing rates continue to remain very high in certain areas across the country. In 2017, according to the CDC, "In 16% of U.S. counties, enough opioid prescriptions were dispensed for every person to have one." And "some counties had rates that were seven times higher than that."[32]

iii. In Summit County, Ohio, 98 opioid prescriptions were written per 100 persons in 2012.[33] In 2017, that number decreased to 62 opioid prescriptions per 100 persons, still above the national 2017 average.[34]

iv. In Cuyahoga County, Ohio, 76 opioid prescriptions were written per 100 persons in 2012.[35] In 2017, that number decreased to 50 opioid prescriptions per 100 persons, below the national average,[36] but still many times greater than prescribing rates in the early 1990's.

v. Among 48 million individuals with any period of insurance coverage between January 2007 and December 2016, including commercial beneficiaries, Medicare Advantage beneficiaries aged 65 years and over, and Medicare Advantage beneficiaries under age 65 years (eligible owing to permanent disability), data show that prescription opioid use and average daily dose measured at the individual level have not substantially fallen from their peaks. "Across all years of the study, annual opioid use prevalence was

[31] Centers for Disease Control and Prevention. *U.S. Prescribing Rate Maps.* https://www.cdc.gov/drugoverdose/maps/rxrate-maps.html
[32] *Id.*
[33] Centers for Disease Control and Prevention. *U.S. County Prescribing Rates, 2012. Maps,* https://www.cdc.gov/drugoverdose/maps/rxcounty2012.html
[34] Centers for Disease Control and Prevention. *U.S. County Prescribing Rates, 2017.* https://www.cdc.gov/drugoverdose/maps/rxcounty2017.html
[35] CDC, 2012 Maps, fn. 33, above.
[36] CDC, 2017 Maps, fn. 34, above.

14% for commercial beneficiaries, 26% for aged Medicare beneficiaries, and 52% for disabled Medicare beneficiaries."[37]

3. The Pharmaceutical Opioid Industry increased sales of prescription opioids by directly targeting doctors, by promoting key opinion leaders, by infiltrating continuing medical education courses, by supporting professional medical societies, and by co-opting medical watchdog organizations like The Joint Commission, to convince prescribers that liberal opioid prescribing is based on science. In fact there has never been sufficient evidence to justify widespread opioid prescribing. These actions directly contributed to the opioid epidemic we face today.

a. Key opinion leaders

i. To encourage doctors to prescribe more opioids, opioid manufacturers promoted the careers of physicians who were sympathetic to their cause. They singled out vocal proponents of liberal opioid prescribing, especially for chronic pain conditions, and paid these physicians to promulgate the benefits of opioids while minimizing the risks.[38]

ii. These "thought leaders" and others, including the Defendant manufacturers, actively promoted a 1980 *New England Journal of Medicine* Letter to the Editor by Porter and Jick, entitled "Addiction Rare in Patients Treated with Narcotics."[39] Porter and Jick described that among hospitalized patients taking opioids for pain, they found only four cases of addiction among 11,882 patients treated with opioids. This letter was used as evidence by Defendants and key opinion leaders to argue that opioid addiction is rare in the course of medical treatment, despite the fact that the so-called evidence was of poor quality and not representative of patients seen in usual clinical care. The catch phrase "less than 1% get addicted," based on this one data point, was used in branded advertisements by opioid manufacturers. (See Appendix I on promotional material.)

iii. Significantly, the population in question in the Porter and Jick article is described as "hospitalized," and receiving at least one dose of an opioid, without any reference to the size of the dose or range of duration of exposure. There is no reasonable basis to compare the risk of addiction among hospitalized patients who may have received only a single dose or short term course of

[37] Jeffery MM, Hooten WM, Henk HJ, *et al.* Trends in opioid use in commercially insured and Medicare Advantage populations in 2007-16: retrospective cohort study. *Bmj*. 2018;362:k2833. doi:10.1136/bmj.k2833, at p. 1.
[38] Saper JR. The Influence of Pharma and Device Manufacturers on APS and other PMAs: A War Within a War. *Exhib 6 to Saper Depos*, at 3-4.
[39] Porter J, Jick H. Addiction rare in patients treated with narcotics. *N Engl J Med*. 1980;302(2):123.

opioid medication, with the far greater risk among patients prescribed opioids for non-cancer chronic pain, outside the hospital setting. This is especially true in light of the well-known relationship between longer duration of opioid exposure and increased risk of dependence and abuse.

iv. As Edlund *et al.* state, "Clinicians should be aware that as they proceed from acute to chronic opioid therapy, the evidence of efficacy decreases whereas the opioid use disorder (OUD) risk increases substantially."[40] For low dose (1-36 MMEs per day) chronic exposure to prescribed opioids, the odds ratio of developing OUD compared to those not prescribed opioids was 14.92 (95% CI = 10.38, 21.46); for medium dose (36-120 MMEs per day) chronic exposure to prescribed opioids, the odds ratio of developing OUD was 28.69 (95% CI = 20.02, 41.13); for high dose (> 120 MMEs per day) chronic exposure to prescribed opioids, the odds ratio of developing OUD was 122.45 (95% CI = 72.79, 205.99).[41]

v. These data from the Edlund study show that both dose and duration affect the risk of opioid use disorder. That is, the higher the dose, the greater the risk; and the longer the duration of exposure; the greater the risk. When both higher dose and longer duration are found, patients are 120 times more likely to suffer from opioid use disorder than patients who were not prescribed opioids.

vi. Despite the lack of reasonable or scientific basis for using Porter and Jick to support the concept of the "rarity" of addiction, Defendants and their key opinion leaders frequently cited this letter to the editor as if it provided sound scientific support for wide prescribing of opioids. (See Appendix I on promotional material.)

vii. Other articles cited by key opinion leaders and Defendants on low addiction rates in pain patient populations, included a national survey of burn facility staff with knowledge of >10,000 burn patients administered opioids, with no cases of iatrogenic addiction identified.[42] Burn debridement, consisting of the removal of dead tissue to promote healing, is a short-term procedure carried out in a hospital setting. Mean administered morphine during the procedure

[40] Edlund, *et al.*, Role of Opioid Prescription," fn. 25, above, at p. 561,
[41] *Id.* at p. 559-60.
[42] Perry, S, Heidrich, G, Management of pain during debridement: A survey of U.S. burn units. *Pain.* 1982;13(3):267-280, http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed1a&NEWS=N&AN=1982178505 . at. 267-77.

was only 8.9 mg, a very low dose. Although the authors referred to continued narcotic therapy after debridement, no details were provided regarding dose or duration, and burn healing is inherently a time-limited process unlike chronic arthritis, back pain, or other conditions for which Defendants promoted opioid therapy. As in the case of the Porter and Jick letter, the low risk of addiction for a short-term, hospital-based procedure and its limited sequelae are not comparable to the significant risk of addiction with long-term opioid therapy for chronic pain, and it is misleading to cite the burn study to support a claim of low addiction risk of opioids. Further, the study was not *a priori* designed to study addiction outcomes, and did not use rigorous methodology to study this outcome.

viii. Defendants and their key opinion leaders also cited a survey study of a large headache clinic by Medina, *et al.* , in support of the claim that risk of addiction was low.[43] Sixty-two patients fulfilled criteria for inclusion in the study, in that they had been prescribed either a narcotic (codeine or propoxyphene), or a barbiturate (butalbital) or both. 38 of the 62 patients were treated with butalbital, a Schedule III medication in the class of barbiturates, and 6 were treated with propoxyphene (Darvon), a Class IV drug. The authors reported, "Eight were dependent; six physically addicted, two psychologically dependent and two were abusers…..There is danger of dependency and abuse in patients with chronic headaches" (p. 1; emphasis added). Reliance upon the Medina study to suggest absence of risk appears to contradict the interpretation of the data by the authors themselves, who explicitly acknowledged the dangers. The authors also used conflated definitions of dependence, addiction, and 'abuse' not consistent with other studies or with DSM criteria of any edition; however, the finding that two patients were "psychologically dependent" would generally have been considered equivalent to a diagnosis of "addiction" at the time of the Medina article. In addition, the study did not use objective criteria for tracking misuse, such as urine toxicology or collateral information from family or the prescription drug monitoring database, which would have increased the investigators' likelihood of identifying aberrant behavior.

ix. None of these surveys represents reliable evidence of a low risk of addiction to prescribed opioids, which even industry key opinion leader, Dr. Russell Portenoy conceded in 2011. In a taped interview with Dr. Portenoy in 2011, Portenoy described his promotion of opioids in the 1990s and early 2000s: "I gave so

[43] Medina JL, Diamond S. Drug Dependency in Patients with Chronic Headaches. *Headache J Head Face Pain*. 1977;17(1):12-14. doi:10.1111/j.1526-4610.1977.hed1701012.x, at pp. 1-2.

many lectures to primary care audiences in which the Porter and Jick article[44] was just one piece of data that I would then cite. I would cite 6 to 7 maybe 10 different avenues of thought or evidence, *none of which represents real evidence*. And yet what I was trying to do was to create a narrative so that the primary care audience would look at this information *in toto* and feel more comfortable about opioids in a way they hadn't before. . . . Because the primary goal was to de-stigmatize, *we often left evidence behind*."[45] (Emphasis added.)

b. Continuing medical education

i. The practicing physician relies on continuing medical education (CME) conferences to acquire state of the art knowledge about the latest scientific evidence in medical practice. The average clinician busy seeing patients cannot wade through the voluminous literature him or herself. Instead, (s)he attends CME conferences, and assumes that the knowledge disseminated there, especially by esteemed academic colleagues, represents unbiased research. The FDA hires independent auditors to review CME courses to make sure they're following a blueprint and are free of pharmaceutical influence, but auditors are required to audit no more than 10% of all CME.[46] (See discussion of one example of an opioid CME designed by Mallinckrodt, in Appendix I)

ii. Drug company–sponsored continuing medical education (CME) preferentially highlights the sponsor's drug(s) compared with other CME programs. The average physician attending CME courses underestimates the influence of industry-sponsored speakers and industry-sponsored CME, which is considerable. Data show changes in prescriber practice in favor of the sponsor's drug, after participation in an industry sponsored CME event.[47]

iii. Not only has drug-company involvement in continuing medical education programs become prolific generally over the past several decades, but Defendants employed CME as part of the strategy to deploy their message about opioids starting in the late 1990s and continuing to today.[48]

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[44] Porter, Jick, *et al.*, "Addiction Rare," fn. 39, above.
[45] Lurie J. Doctors Receive Opioid Training. Big Pharma Funds It. What Could Go Wrong? *Mother Jones*. https://www.motherjones.com/politics/2018/04/doctors-are-required-to-receive-opioid-training-big-pharma-funds-it-what-could-go-wrong/.
[46] *Id.* at p. 3.
[47] Wazana A. Physicians and the pharmaceutical industry: Is a gift ever just a gift? *JAMA*. 2000;283(3):373-380. http://dx.doi.org/10.1001/jama.283.3.373, at pp. 373, 377-78.
[48] Saper, "The Influence of Pharma," fn.38, above, at p. 2.

iv. I have personally experienced this CME strategy. For example, in 2001, every licensed physician in the state of California was mandated to attend a day-long CME course on the treatment of pain as a requirement to maintain licensure. I attended that day-long course, in which use of opioids was promoted. I recall that there was no accurate presentation of the risks of opioids, and the messages that were provided tracked the misconceptions described above regarding overstatement of the benefits of opioids.

v. Consistent with and supportive of my personal experience, Dr. Joel Saper, a past board member of the American Pain Society (APS), testified that "the educational programs of AAPM [American Academy of Pain Management] and APS particularly as they involve opioid advocacy, were greatly influenced by commercial largess. In my opinion, commercial dynamics influenced, if not steered, the selection of abstracts, course topics, and faculty to commercially friendly participants as it involved opioid advocacy, largely ignoring those imposing or exhorting caution against the growing advocacy for opioids for chronic nonmalignant pain.[49] Dr. Saper testified that such educational programs of AAPM and APS involving opioid advocacy were "inappropriate"[50] , and I agree.

vi. Dr. Saper further stated that "APS and AAPM and its members have participated, if not promoted, this crisis by failing to assure the presentation of unbiased, balanced educational programs and guideline development, thereby protecting the public from commercial influence through undisclosed support from the opioid industry. In failing to do so, the organizations failed to protect patients."[51]

vii. Further, an internal Purdue Pharma email from Richard Sackler to Paul Goldenheim, dated April 13, 2001, concerned a planned meeting with "leaders of APS, APF [American Pain Foundation] and other pain societies." Dr. Sackler stated, "Our goal is to bind these organizations more closely to us than heretofore, but also to align them with our expanded mission and to see that the fate of our product(s) are [sic] inextricably bound up with the trajectory of the pain movement."[52]

viii. The use of "Speakers Bureaus" of doctors, trained by a drug company to promote its product, is an adjunct to the CME strategy.

[49] Deposition of Joel R. Saper, M.D., January 11, 2019, MDL No. 2804, at 92:13-22.
[50] *Id.* at 93:15-19.
[51] *Id.* at 115:24-116:6
[52] PPLPC045000004928- PPLPC045000004933 at 4929.

> "From 1996 to 2001, Purdue conducted more than 40 national pain-management and speaker-training conferences at resorts in Florida, Arizona and California. More than 5000 physicians, pharmacists, and nurses attended these all-expenses paid symposia, where they were recruited and trained for Purdue's national speaker bureau. It is well-documented that this type of pharmaceutical company symposium influences physicians' prescribing, even though the physicians who attend such symposia believe that such enticements do not alter their prescribing patterns."[53]

ix. These documents and testimony support my opinion that the Pharmaceutical Opioid Industry improperly supported the pro-opioid mis-education of medical professionals in order to increase sales of prescription opioids that resulted in an unprecedented epidemic of drug-induced mortality and morbidity. As I have written and stated elsewhere, doctors must bear some responsibility for the over-prescribing of opioids for chronic pain. However, the Pharmaceutical Opioid Industry bears the far greater share of the responsibility, for its role in promoting false messages of substantial benefit and low risk of opioids that influenced doctors to prescribe.

c. The Joint Commission sold industry-produced teaching materials to hospitals.

i. The Joint Commission on Accreditation of Healthcare Organizations (JCAHO), often simply referred to as "The Joint Commission" (TJC), is a United States–based nonprofit tax-exempt 501(c) organization that accredits health care organizations and programs in the United States. The Joint Commission arose out of a movement in the 1950s to reform hospitals by looking at whether or not patients got better. JCAHO went through a consolidation of power over the years, combining multiple medical organizations under one roof, simplifying its name in 2007 to "The Joint Commission." Its positioning statement is "Helping Health Care Organizations Help Patients."[54]

ii. Today, having Joint Commission accreditation is required for many hospitals and clinics to remain licensed. Payment for services from the Centers for Medicare and Medicaid Services (CMS), the largest federally funded insurance program, is also

[53] Van Zee A. The promotion and marketing of oxycontin: Commercial triumph, public health tragedy. *Am J Public Health*. 2009. doi:10.2105/AJPH.2007.131714, at pp.221-22.
[54] The Joint Commission. http://www.jointcommission.org/ . Accessed September 2, 2015.

contingent on TJC approval. TJC approval is obtained through periodic surveys.

iii. The Joint Commission sold educational materials to hospitals so they could meet the standards of pain treatment that would be required to pass the next Joint Commission Survey. These materials included laminated cards and posters of the Visual Analog Scale of pain, as well as teaching videos promoting more liberal prescribing of opioids for pain, including misleading statements such as: "Some clinicians have inaccurate and exaggerated concerns about addiction, tolerance and risk of death. . . . This attitude prevails despite the fact there is no evidence that addiction is a significant issue when persons are given opioids for pain control."[55] Per the GAO 2003 report, "During 2001 and 2002, Purdue funded a series of nine programs throughout the country to educate hospital physicians and staff on how to comply with JCAHO's pain standards for hospitals and to discuss postoperative pain treatment. Purdue was one of only two drug companies that provided funding for JCAHO's pain management educational programs. Under an agreement with JCAHO, Purdue was the only drug company allowed to distribute certain educational videos and a book about pain management; these materials were also available for purchase from JCAHO's Web site. Purdue's participation in these activities with JCAHO may have facilitated its access to hospitals to promote OxyContin."[56]

iv. On December 31, 2000, an internal Purdue email from Robin Hogen to Mortimer Sackler, MD, responded to Dr. Sackler's assertion that more articles were needed "to help counteract the negative articles in the national media." Hogen's email, re press coverage of JCAHO pain guidelines, stated, "With respect to generating more articles about pain guidelines, we 'loaned' JCAHO our PR firm (Fleishman Hillard) last year during the national roll out of the new standards. I suspect some of these stories which are now breaking at year-end were generated by media contacts made several months ago. We could certainly renew that grant ($75k) this year- to generate as much positive, unbranded publicity about the new pain standards and the chronic undertreatment of pain in America. Good idea." This exchange supports my opinion that the Pharmaceutical Opioid Industry played a significant, insidious role in the epidemic of over-

[55] Catan T, Perez E., A Pain Drug Champion Has Second Thoughts. *The Wall Street Journal*. December 2012, at p.4.

[56] GAO. Prescription OxyContin Abuse and Diversion and Efforts to Address the Problem. *J Pain Palliat Care Pharmacother*. 2003;18(3):109-113. doi:10.1300/J354v18n03_12, at p.23.

prescribing of opioids, by funding the widespread promotion of standards that mandated pain treatment, while the medical profession and the public were unaware of Industry's hidden role.[57]

4. The Pharmaceutical Opioid Industry encouraged and promoted several misconceptions concerning opioid use, including overstatement of benefits of long-term use for chronic pain. In fact, there is not, and has never been, reliable evidence that long-term opioid use improves pain or function to any clinically meaningful degree. The best evidence available suggests that there is little or no improvement in pain or function for most patients on long-term opioid therapy. The Industry further claimed that the failure to prescribe opioids led to the 'undertreatment of pain.' Whether or not pain was undertreated does not change the fact that prescription opioids are an inappropriate method to address that concern, due to the absence of evidence of long-term benefit, and the strong evidence of unacceptable risk. Further, patients often endorse ongoing subjective benefit from the opioid, not because it is treating underlying pain, but because it is relieving opioid withdrawal from the previous dose. Studies show that pain improves when patients on chronic high dose opioid therapy reduce their dose or come off opioids. Limiting opioid prescribing is good medicine, because it decreases exposure to a dangerous and potentially lethal drug, without compromising pain treatment.

a. Scientific evidence of prescription opioids' benefit for chronic pain has been repeatedly described as "weak," or "inconclusive." Randomized, placebo-controlled clinical trials, generally 12 weeks or less, were too brief to support claims of long-term benefit, and non-randomized trials do not provide reliable evidence of efficacy. Such evidence was inadequate to support the widespread use of the drugs and the risks they imposed. Even the 2009 Guidelines promulgated by advocacy groups funded by the Pharmaceutical Opioid Industry admitted that evidence regarding chronic opioid therapy was "insufficient to assess effects on health outcomes."[58] Twelve-week studies of opioids are insufficient to assess their risks and benefits, for the following reasons:

i. Prescription opioids differ from other pain medications in important ways. In addition to providing acute pain relief, opioids also have unintended psychotropic effects (improved mood, increased energy, decreased anxiety), which make them more likely to be reinforcing and to lead to addiction. Patients with chronic pain can find opioids reinforcing, independent of whether they provide pain relief.[36] (p. 8) Although addiction to opioid painkillers can occur quickly in some individuals, for others, addiction may take weeks or months to manifest, and duration of exposure is the most significant risk factor for addiction (see discussion of Edlund study,[20] above). Hence, a true assessment of the risks of highly addictive drugs like opioid pain relievers, (the

[57] PDD8801183361- PDD8801183364 at 3363

[58] Chou R. Clinical Guidelines for the use of chronic opioid therapy in chronic noncancer pain. *Pain*. 2009;10(2):113-130 at p. 130.e5.

molecular equivalent of heroin), requires a longer period of study than 12 weeks.

ii. There are serious and certain risks associated with long term opioid therapy, including but not limited to tolerance, dependence, withdrawal, opioid induced hyperalgesia, immunosuppression, serious constipation, depression, cognitive decline, cardiac effects, breathing effects, hormonal effects, depression, addiction, accidental overdose, and death, reflecting a low benefit to risk ratio for long term opioid therapy.[59] These risks increase with increasing dose and duration of the drug.[60] Hence, the high risks associated with opioids, necessitate a longer study period to assess the true benefit-risk ratio for all patients.

b. A series of reviews, including several in the Cochrane Database, have reached similar conclusions regarding the inadequacy of the scientific evidence of long-term opioid therapy for chronic non-cancer pain.

i. The 2010 Cochrane (Noble 2010) review found that there was only "weak" evidence to support the use of opioids for chronic non-cancer pain.[61]

A. "All of the evidence bases considered in this systematic review were of low internal validity and therefore at potentially high risk of bias." Reasons for this assessment included the funding source ("Only two studies did not clearly have a funding source with a potential conflict of interest in the findings (e.g., drug company) [p. 9]," failure to compare characteristics of dropouts to those of patients who completed the studies; and failure to describe recruitment methods. The highest risk of bias existed for the "continuous outcomes" of pain relief and quality of life, because "high attrition rates affect both the risk of bias and the generalizability of the results from the continuous data outcomes."[62]

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[59] Lembke *et al.*, "Weighing The Risks," fn. 3, above, at p. 985; *see also* Chou R, Deyo R, Devine B, *et al.* The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain. Evid Rep Technol Assess (Full Rep). 2014;218(218):63. doi:10.23970/AHRQEPCERTA218 at p. ES-1; *see also* Edelman EJ, Gordon KS, Crothers K, *et al.* Association of Prescribed Opioids with Increased Risk of Community-Acquired Pneumonia among Patients with and Without HIV. JAMA Internal Medicine. 2018, at p. 298.
[60] Chou R, Turner J a., Devine EB, *et al.* The Effectiveness and Risks of Long-Term Opioid Therapy for Chronic Pain: A Systematic Review for a National Institutes of Health Pathways to Prevention Workshop. Ann Intern Med. 2015;162(4). doi:10.7326/M14-2559, p. 283
[61] Noble M, Treadwell JR, Tregear SJ, *et al.* Long-term opioid management for chronic noncancer pain. Cochrane Database Syst Rev. 2010;(1):CD006605. doi:10.1002/14651858.CD006605.pub2, p. 2.
[62] *Id.* at pp. 7-8.

B. At pp. 9-14, specific data on attrition were provided: For the "strong opioid" category (categories described at p. 7), including extended release morphine, controlled release oxycodone, extended release oxymorphone, extended release tramadol and methadone; for oral medications, 34.1% discontinued due to adverse effects and 10.3% discontinued due to insufficient pain relief, for a total of 44.4% who discontinued strong oral opioids.[63]

C. The review states that only 273 (58%) of those who began the long-term extensions of short-term trials remained in the study at the 6-7.5 month cut-off point where data were available for all 3 oral opioid studies. "Because the attrition rate is so high, the participants are likely highly selected, and the data may be biased."[64]

D. The authors report pain relief for those able to remain on oral opioids for 6 months; however: "The strength of the evidence supporting this conclusion is weak."[65]

E. Quality of Life (QoL):

I. For oral morphine: A single study (Allan, 2005), reporting a "small improvement on the mental subscale and a larger improvement of the physical subscale" provided an "insufficient quantity of data from which to draw conclusions."[66]

II. QoL improvement was "weakly supported" with transdermal fentanyl (TDF).[67]

III. For QoL with intrathecal opioids, there were inconsistent findings "No conclusions can be drawn."[68]

F. "Data describing long-term safety and efficacy of opioids for CNCP are limited in terms of quantity and quality. An evidence base consisting of low-quality studies provides only *weak evidence* from which to draw qualitative

[63] *Id.* at pp. 9-14.
[64] *Id.* at p. 15.
[65] *Id.* at p. 16.
[66] *Id.* at p. 20.
[67] *Id.* at p. 21
[68] *Id.* at p. 22

conclusions and only low-stability evidence from which to draw quantitative conclusions." (Emphasis added.)[69]

G. "Despite the identification of 26 treatment groups with 4768 participants, the evidence regarding the effectiveness of long-term therapy in CNCP was too sparse to draw firm conclusions."[70]

ii. Another Cochrane Review of opioids in the treatment of chronic low back pain (CLBP) (Chaparro 2013) found, "There is some evidence (*very low to moderate quality*) for short-term efficacy (for both pain and function) of opioids to treat CLBP compared to placebo."[71] (Emphasis in original.)

A. "The very few trials that compared opioids to non-steroidal anti-inflammatory drugs (NSAIDs) or antidepressants did not show any differences regarding pain and function. The initiation of a trial of opioids for long-term management should be done with extreme caution, especially after a comprehensive assessment of potential risks."[72]

B. "There are no placebo-RCTs supporting the effectiveness and safety of long-term opioid therapy for treatment of CLBP…. We have no information from randomized controlled trials supporting the efficacy and safety of opioids used for more than four months. Furthermore, the current literature does not support that opioids are more effective than other groups of analgesics for LBP such as anti-inflammatories or anti-depressants."[73]

iii. Another Cochrane review (McNicol 2013) found: "While intermediate term studies all indicated that opioids were better than placebo, most studies were small, most were short, and none used methods known to be unbiased. All these features are likely to make effects of opioids look better in clinical trials than they are in clinical practice."[74] Note that the McNicols review defined "intermediate" term studies as 35-84 days (ie, 5-12 weeks). Accordingly, these so-called intermediate studies are actually 12

[69] *Id.* at p. 23.
[70] *Id.* at p. 25.
[71] Chaparro LE, Furlan AD, Deshpande A, Mailis-Gagnon A, Atlas S, Turk DC. Opioids compared to placebo or other treatments for chronic low-back pain. Cochrane Database Syst Rev. 2013. doi:10.1002/14651858.CD004959.pub4, at p. 2
[72] *Id.*
[73] *Id.*
[74] McNicol E, Midbari A, Eisenberg E. Opioids for neuropathic pain (Review). *Cochrane Database Syst Rev*. 2013. doi:10.1002/14651858.CD006146.pub2, at p. 3

weeks or less, therefore too brief to provide data relevant to efficacy for chronic pain.[75]

iv. Another 2014 Cochrane review reached similar conclusions: "Similar to previous systematic reviews of randomized trials on opioid therapy for non-cancer pain [cites omitted], we found that most of the trials included in our review had a treatment duration of several days or a few weeks only."[76]

A. "Although some of the newer trials in the update had slightly longer treatment durations [cites omitted], in none of the trials did the participants receive opioids for longer than six months. This is still too short to address the impact of opioid treatment on routine clinical practice in the treatment of a chronic condition such as osteoarthritis. While no evidence of long-term effects is available from randomized trials, observational studies indicate that long-term treatment with opioids of chronic conditions such as osteoarthritis may have deleterious effects and do not seem to improve pain relief [citation omitted]"[77](emphasis added).

B. Reviewers found that the "small mean benefit" was "contrasted by significant increases in the risk of adverse events. For the pain outcome in particular, observed effects were of questionable clinical relevance since the 95% CI [confidence interval] did not include the minimally clinically important difference" on a visual analog scale.[78]

v. Chou *et al.* in their 2015 systematic review on the effectiveness of opioids in the treatment of chronic pain stated: "Evidence is *insufficient* to determine the effectiveness of long-term opioid therapy for improving chronic pain and function. Evidence supports a dose-dependent risk for serious harms." [79] (Emphasis added.) The authors reported that most placebo-controlled studies were less than 6 weeks, and none were over 16 weeks long. "We did not include uncontrolled studies for these outcomes; reliable conclusions cannot be drawn from such studies because of the lack

[75] *Id.* at p. 13.
[76] da Costa BR, Nuesch E, Kasteler R, *et al.* Oral or transdermal opioids for osteoarthritis of the knee or hip (Cochrane Review). 2014, at p. 28.
[77] *Id.*
[78] *Id.* at p. 2.
[79] Chou *et al.*, "Effectiveness and Risks – Systemic Review," fn. 60, above, at p. 276.

of non-opioid comparison group and heterogeneity of the results."[80]

vi. In 2009, Chou was the lead author of a panel made up of a majority of Industry-funded physicians and psychologists who promulgated Guidelines that allowed for the use of chronic opioid therapy; in the same publication, those authors admitted that evidence regarding chronic opioid therapy was "insufficient to assess effects on health outcomes."[81]

vii. In another systematic review of opioid and non-opioid medication for acute or chronic low back pain, Chou *et al.* found that evidence for opioids "remains limited to short term trials showing modest effects versus placebo for chronic low back pain." Shortcomings of the studies included high attrition (30-60% in most trials) and "short follow-up" (one at 16 weeks, all others shorter).[82] Authors also noted: "Trials were not designed to assess the risk for overdose or opioid use disorder because of relatively small samples, short follow up, and exclusion of higher risk patients; in addition, many studies used an enriched enrollment randomized withdrawal design which could underestimate harms." [83] (See paragraphs 9a-d, below, for discussion of enriched enrollment study design).

viii. In a systematic review and meta-analysis (Häuser, Schmerz, 2015) of open-label continuation trials up to 26 weeks in duration in patients with a variety of different chronic pain disorders, the authors state "… the risk of bias [for these studies] was high …. all studies were funded by the manufacturers of the drugs[84]…. average pain scores are unrepresentative of patient experience and of very limited utility[85]…. The positive effects of opioid in long-term open-label studies cannot be disentangled from those of co-therapies not controlled for, from unspecific (placebo) effects because of the lack of placebo group or from the spontaneous recovery because of the lack of no treatment group. The external validity of open-label extension studies was comprised [sic] by a highly selected group of patients without major medical disease or

[80] *Id.* at p. 280
[81] Chou, *et al.*, "Clinical Guidelines," fn. 58, above, at p. 130.e5.
[82] Chou R, Deyo R, Friedly J, *et al.* Systemic pharmacologic therapies for low back pain: A systematic review for an American College of physicians clinical practice guideline. Ann Intern Med. 2017. doi:10.7326/M16-2458, at p. 483.
[83] *Id.* at p. 486.
[84] Häuser W, Bernardy K, Maier C. Long-term opioid therapy in chronic noncancer pain: A systematic review and meta-analysis of efficacy, tolerability and safety in open-label extension trials with study duration of at least 26 weeks. Schmerz. 2015. doi:10.1007/s00482-014-1452-0, at p. 4.
[85] *Id.* at p. 7

mental disorders. The self-selected group of patients who were willing to participate in the open-label extension studies does not permit a clear conclusion on the long-term efficacy of opioids in routine clinical care."[86]

ix. Many studies used an enriched enrollment randomized withdrawal (EERW) study design, an inherently biased methodology which *a priori* favors opioids over placebo. EERW design selects patients who are predisposed to tolerate and prefer opioids, and hence are not reflective of the general clinical population.

A. Randomized, double blind, placebo-controlled trials of 12 weeks durations or less (15 studies total) of opioids in the treatment of chronic pain used to get FDA approval, relied on enriched enrollment design (Meske *et al.* 2018),[87] and hence were biased toward favoring opioids. Open-label continuation trials commonly included subjects who successfully completed the randomized controlled trial phase using an enriched enrollment design. Hence those who entered the open label phase included those who successfully tolerated opioids through the randomized controlled trial period, resulting in an additional layer of bias favoring opioids, and diminishing the applicability of the study results to real world conditions.

B. For example, of the 295 initial subjects in the study by Caldwell *et al.* (2002)' 222 subjects were assigned to opioid groups and 73 were assigned to placebo.[88] A 4-week randomized controlled trial (RCT) preceded an open-label phase; 40% of the opioid group who participated in the RCT dropped out due to adverse effects or inadequate pain relief,[89] and only those who lasted the full four weeks were permitted to enter the open-label phase. Of the 184 subjects who entered the open-label phase, 131 (72%) came from the opioid groups, while only 50 (28%) came from the placebo group; therefore, the open-label phase included a large majority of subjects who had demonstrated the capability to tolerate opioids, and the study's claims of

[86] *Id.* at p. 8.
[87] Meske DS, Lawal OD, Elder H, Langberg V, Paillard F, Katz N. Efficacy of opioids versus placebo in chronic pain: A systematic review and meta-analysis of enriched enrollment randomized withdrawal trials. J Pain Res. 2018. doi:10.2147/JPR.S160255, at pp. 923-934
[88] Caldwell JR, Rapoport RJ, Davis JC, *et al.* Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: Results from a randomized, placebo-controlled, double-blind trial and an open-label extension trial. J Pain Symptom Manage. 2002. doi:10.1016/S0885-3924(02)00383-4, at p. 283
[89] *Id.* at p. 283.

efficacy are not transferable to a real-world population. Despite the bias favoring opioid-tolerant subjects, more than half failed to complete the open-label phase; 95/181 (52.5%) discontinued.[90]

C. A meta-analysis of short term studies (< 6 weeks) confirmed a difference between enriched enrollment studies and non-enriched enrollment studies in terms of adverse medical consequences: "The incidence of adverse effects was noticeably different in the trials that used a classical non-EERW design from those that used the EERW design (Table 3). Among the trials with a non-EERW design, the number of reported adverse effects was 26, while among the trials with an EERW design, only eight adverse effects were reported."[91]

c. A recent (Busse 2018) metaanalysis confirms that there are no data to show clinically significant long-term efficacy of opioids in the treatment of chronic pain.[92]

i. The primary study outcomes were "pain relief, physical functioning, and vomiting".[93] The study defined the term Minimally Important Difference (MID) as "the smallest amount of improvement in a treatment outcome that patients would recognize as important."[94] The data showed that opioid therapy failed to meet the MID as to the primary outcomes of pain relief and physical functioning, as well as the secondary outcomes of emotional functioning, social functioning, or sleep quality compared to placebo.[95]

ii. For pain relief, the MID was defined as 1 cm on the 10 cm Visual Analog Scale (VAS); the data showed that the difference between opioid therapy and placebo was only 0.79 cm on the VAS, thus no minimally important difference was shown.[96] Despite not meeting the standard, the authors state, "Although the difference did not meet the minimally important difference of 1 cm, opioids were

[90] *Id.* at p .286.
[91] Furlan AD, Chaparro LE, Irvin E, Mailis-Gagnon A. A comparison between enriched and nonenriched enrollment randomized withdrawal trials of opioids for chronic noncancer pain. Pain Res Manag. 2011;16(5):337-351. doi:10.1155/2011/465281, at p. 347.
[92] Busse JW, Wang L, Kamaleldin M. Opioids for Chronic Noncancer Pain: A Systematic Review and Meta-analysis. JAMA. 2018;320(23):2448-2460. doi:10.1001/jama.2018.18472.
[93] *Id.* at p. 2449.
[94] *Id.* at p. 2450.
[95] *Id.* at pp. 2451, 2455.
[96] *Id.* at p. 2451.

associated with pain relief compared to placebo…."[97] A more accurate statement would be that opioids were associated with a clinically insignificant difference in pain relief, since the change did not meet the study's own definition of a clinically significant difference.. The study reported a difference of 2.80 favoring opioids over placebo on a 100-point scale for "role functioning;" however, "[w]hen restricted to trials reporting actual change, high quality evidence from 16 RCTs (5329 patients) demonstrated no association of opioids on role functioning compared to placebo."[98]

iii. For the primary endpoint of vomiting, the opioid subjects had more than a 4-fold greater risk in nonenrichment trials, and a 2.5 times greater risk in enrichment trials, that is, trials in which subjects were pre-selected for greater ability to tolerate opioid therapy.[99]

iv. As for "Active Comparator" studies, the authors state: Moderate quality evidence [9 RCTs, 1431 patients] showed "no difference in the association of opioids versus nonsteroidal anti-inflammatory drugs for pain relief," (emphasis added), and the same was true for physical function. The only significant difference was over 4-fold greater vomiting with opioids compared to NSAIDs (RR = 4.74, $p \leq 0.001$).[100]

v. Although the goal was to assess "chronic" non-cancer pain, the authors acknowledge that "it was not possible to assess the long-term associations of opioids with chronic non-cancer pain because no trial followed up patients for longer than 6 months."[101] (Emphasis added). There is some inconsistency in the literature about the definition of "chronic." For example, the Cochrane Review (Noble, 2010) cites the International Association for the Study of Pain (IASP) for a definition of "pain which persists past the normal point of healing," considered to be 3 months[102]; however, on the very next page, the Cochrane review states that it considered only studies of at least six months, which it termed "Chronic opioid use…".[103] In any case, the Busse authors' statement that it could not be applied to "long-term" use is an important limitation.

vi. The Busse study states, "Studies with longer follow-up reported less relief," which provides significant support for the reduced pain

[97] *Id.* at pp. 2451-2452.
[98] *Id.* at pp. 2451, 2455.
[99] *Id.* at p. 2455.
[100] *Id.*
[101] *Id.* at p. 2457.
[102] Noble, *et al.*, "Long Term Opioid Management," fn 61, above, at p. 2.
[103] *Id.* at pp. 3, 6.

relief of opioids over time, and which buttresses the conclusion that even the minor "improvements" in pain and physical function shown in the studies compiled by Busse, which had a median of only 60 days' follow-up,[104] cannot be extrapolated to longer term opioid use.

vii. Three quarters of the studies 76 (79%) reported receiving industry funding.[105]

viii. Despite these limitations, the authors concluded: "… some patients may find the modeled proportion of 12% for achieving the minimally important difference for pain relief warrants a trial of treatment with opioids." The figure of 12% appears to represent the difference between the percentage who reported MID pain relief on placebo (48.7%) and those who reported MID pain relief on opioid therapy (60.6%); difference = 11.9%.[106]

ix. In sum, the Busse analysis stands for the proposition that, by submitting to opioid therapy, the patient incurs significant and potentially fatal risks, in exchange for "benefits" that are found to be comparable to placebo for the large majority of subjects studied.

x. The pain relief MID standard adopted in the Busse study was at the low end of the spectrum of such study definitions, meaning that less improvement was required to meet the MID standard. A pooled analysis of multiple pain studies found that the average MID was 17 mm (1.7 cm) on the VAS scale, or over twice the 0.79 cm difference reported in the Busse meta-analysis.[107] Despite the lenient standard to show a difference that patients would notice, the Busse results failed that test.

d. The SPACE randomized clinical trial study, published in JAMA in 2018, comparing opioid and non-opioid medication in the treatment of chronic pain, is the first long term (one year) randomized controlled trial of opioids in the treatment of moderate to severe pain, and found no benefit of opioids over non-opioid medication.[108]

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[104] Busse, *et al.*, "Opioids for Chronic Noncancer Pain," fn 92, above, at p. 2451.
[105] *Id.* at p. 2451.
[106] *Id.* at p. 2456.
[107] Olsen MF, Bjerre E, Hansen MD, *et al.* Pain relief that matters to patients: Systematic review of empirical studies assessing the minimum clinically important difference in acute pain. BMC Med. 2017. doi:10.1186/s12916-016-0775-3, at p. 10.
[108] Krebs EE, Gravely A, Nugent S, *et al.* Effect of opioid vs nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain the SPACE randomized clinical trial. JAMA - J Am Med Assoc. 2018. doi:10.1001/jama.2018.0899

i. The SPACE trial showed no benefit of opioids over non-opioid medication (NSAIDs, acetaminophen) in the treatment of moderate to severe chronic back, hip, or knee pain. The opioid group had significantly more adverse medication related symptoms.[109]

ii. The SPACE trial used a gold standard study design, as follows. It was 12 months in duration, a sufficient length to assess efficacy in the treatment of chronic pain. It included only patients not previously on long-term opioid therapy, and assessed preference for opioids prior to randomization, thereby eliminating the enriched enrollment bias evident in other studies. It used a naturalistic sample of patients in the primary care setting, including some patients with severe depression and post-traumatic stress disorder, the same patients who are often on high dose long term opioid therapy in real-life.[110] Participants were regularly assessed for medication misuse, including checking the prescription drug monitoring database and urine drug testing.[111] It was not sponsored by an opioid manufacturer.[112]

iii. It is very significant that a gold standard RCT, conducted by independent researchers and published in a leading medical journal (JAMA), reached an opposite result from those claimed by the Pharmaceutical Opioid Industry based on biased, short-term studies conducted by their own employees or paid consultants, and often published in specialty journals. The SPACE trial strongly supports my opinion that chronic opioid therapy does not provide greater long-term efficacy, rendering its high risks all the more unacceptable. Further, other studies have shown that opioids are no better than non-opioids for pain treatment.

A. In the Cochrane Review by Chaparro, *et al.* , discussed above, opioids were not superior to non-opioids for chronic low back pain.[113]

B. In a review of randomized head to head comparisons of opioids vs non-opioid pain relieving medication, non-opioids were found to be superior to opioids in terms of physical function and tolerability for short term (4-12

[109] *Id.* at p. 872.
[110] *Id.* at p. 873
[111] *Id.* at p. 875.
[112] *Id.* at p. 881.
[113] Chaparro, *et al.*, "Opioids Compared to Placebo," fn 71, above, at p. 2.

weeks) therapy of neuropathic, low back, and osteoarthritic pain.[114]

C. A systematic review comparing oral NSAIDS with opioids for treatment of pain due to knee osteoarthritis over at least 8 weeks' duration found opioids were no better than NSAIDs.[115]

e. Despite the absence of reliable evidence for the use of long-term opioid therapy in the treatment of chronic pain, the Pharmaceutical Opioid Industry sought to shame prescribers into opioid prescribing, by claiming that the 'failure' to prescribe opioids was tantamount to causing pain, and to scare them into prescribing by suggesting reprisal from regulatory bodies like The Joint Commission. In their promotional material and "Train the Trainer" course, Defendants frequently invoked sources that characterized opioid prescribing as a moral obligation, and the failure to prescribe as the equivalent of causing pain, leading to Joint Commission and legal sanctions. Below are just a few examples. (See Appendix I for more detail.)

i. I remember that fear of 'undertreating pain' permeated medical practice and culture at this time. Doctors in some states were subject to the risks of disciplinary action from the board, and lawsuits that could follow, if they denied a patient's request for opioids.

ii. Joel Saper, M.D., a past board member of the American Pain Society (APS), testified that the American Pain Society (APS) received financial support from the Opioid Industry, which he referred to as "narcopharma. The American Pain Society, in turn, supported University of Wisconsin Pain and Policy Study Group (PPSG) professors David Joranson and June Dahl to "visit boards of medicine in state after to state to argue the importance of lessening the regulation of doctors who prescribe opioids for cancer, acute, and end-of-life pain."[116]

iii. In addition to the indirect support by the Industry through the APS, direct financial support to PPSG was provided by the Pharmaceutical Opioid Industry, as revealed in documents produced by PPSG and summarized in Appendix II to this Report.

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[114] Welsch P, Sommer C, Schiltenwolf M, Häuser W. Opioids in chronic noncancer pain-are opioids superior to nonopioid analgesics? : A systematic review and meta-analysis. Schmerz. 2015. doi:10.1007/s00482-014-1436-0, at p. 3.

[115] Smith SR, Deshpande BR, Collins JE, Katz JN, Losina E. Comparative pain reduction of oral non-steroidal anti-inflammatory drugs and opioids for knee osteoarthritis: Systematic analytic review. Osteoarthr Cartil. 2016. doi:10.1016/j.joca.2016.01.135, at p. 962.

[116] Saper, "The Influence of Pharma," fn 38, above, at p. 9.

Those documents show substantial contributions by Purdue Pharma, Janssen, Endo, Ortho-McNeil, Alpharma, and Cephalon, over a period of over a decade, during which PPSG justified its recurring requests for further funding on the basis of its successful efforts to loosen restrictions on opioid prescribing by lobbying State Medical Boards, presentations at professional conferences, leading industry-friendly Continuing Medical Education seminars, and publications in the scientific literature. (See Appendix II to this Report).

iv. The Pharmaceutical Opioid Industry and PPSG influenced states to adopt intractable pain laws that encouraged opioid prescribing by shielding physicians from liability. Although the statutes may have initially been intended for cancer, acute, and end-of-life pain, the statutes do not necessarily include any such limitations, and the Ohio statute did not restrict its protective shield to those circumstances. Intractable Pain Laws in various states, including Ohio,[117] strengthened physicians' ability to prescribe opioids and also protected physicians from disciplinary action if the drugs were prescribed in compliance with the terms of the law.

v. Ohio's Intractable Pain Law has since been revised to include a more involved series of steps that a prescribing doctor should take regarding discussion of the risks, monitoring the results, etc. Such belated restrictions were, however, insufficient to unwind the damage done by prior enactment of legislation that encouraged the increased prescribing of opioids. Notably, the PPSG documents include Ohio among the states whose pain laws were "improved" between 2000-2003, where "improvement" included loosening restrictions on opioid prescribing. (See Appendix II).

f. Pain *improves* when patients on chronic high dose opioid therapy reduce their dose or come off of opioids.

i. A retrospective research study of patients consecutively admitted to the Mayo Clinic Pain Rehabilitation Center from 2006 through 2012, with a pain diagnosis of fibromyalgia, showed that patients tapered off of opioids had significant improvements in pain-related measures including numeric pain scores. The authors concluded, "this systemic review suggests that pain, function and quality of life may improve during and after opioid dose reduction."[118]

[117] Ohio Admin. Code §4731-21

[118] Cunningham JL, Evans MM, King SM, Gehin JM, Loukianova LL. Opioid tapering in fibromyalgia patients: Experience from an interdisciplinary pain rehabilitation program. Pain Med (United States). 2016. doi:10.1093/pm/pnv079, at p. 14.

ii. A meta-analysis of opioid legacy patients (patients on long term opioid therapy as a 'legacy' of opioid prescribing in the 1990s) demonstrated that pain improves for many patients who decrease or go off of long term opioid therapy (LTOT). Sixty-seven studies were included in this analysis. Among 40 studies examining patient outcomes after dose reduction, improvement was reported in pain severity (8 of 8 fair-quality studies), function (5 of 5 fair-quality studies), and quality of life (3 of 3 fair-quality studies).[119] The authors repeatedly note the need for more research and better quality evidence. Nonetheless, they conclude "several types of interventions may be effective to reduce or discontinue LTOT and that pain, function, and quality of life may improve with opioid dose reduction."[120]

iii. In a study by Sullivan et al, high dose legacy patients were randomly assigned to a 22-week taper support intervention (psychiatric consultation, opioid dose tapering, and 18 weekly meetings with a physician assistant to explore motivation for tapering and learn pain self-management skills) or usual care (N=35).[121] The authors write, "It is important to note that the opioid dose reduction in both the taper support and usual care groups was achieved without a significant increase in pain severity. In fact, pain severity decreased on average from baseline to 22 weeks by approximately 1 point on the 0–10 scale in the taper support group and approximately a half-point in the usual care group. This finding is consistent with those in studies of inpatient pain rehabilitation programs, which have documented pain reduction with opioid dose reduction ."[57122]

iv. A small outpatient study of opioid tapering in community patients showed no increase in pain intensity scores in patients who were able to taper their opioids by greater than 50% from the starting dose. The median opioid dose in the sample was 288 MED. The median duration of opioids was six years. Median pain intensity was moderate (5 out of 10 on a numeric pain rating). After four months, the median MED was reduced to 150 (IQR, 54-248) mg

[119] Frank JW, Lovejoy TI, Becker WC, *et al.* Patient outcomes in dose reduction or discontinuation of long-term opioid therapy: A systematic review. Ann Intern Med. 2017;167(3):181-191. doi:10.7326/M17-0598, at pp. 185-186.
[120] *Id.* at p. 181.
[121] Sullivan MD, Turner JA, DiLodovico C, D'Appollonio A, Stephens K, Chan Y-F. Prescription Opioid Taper Support for Outpatients With Chronic Pain: A Randomized Controlled Trial. J Pain. 2017. doi:10.1016/j.jpain.2016.11.003, at p. 308.
[122] *Id.* at p. 318.

(P = .002). Of note, neither pain intensity (P = .29) nor pain interference (P = .44) increased with opioid reduction.[123]

v. Many patients on chronic opioid therapy are reluctant to taper. In addition, some physicians and authors question whether tapering is necessary if the patient is stable and adherent to their current dose. Yet it is well established that patients on high doses of opioids are at increased risk for a variety of side effects, serious morbidities, and death. [124] Quality of life may be adversely affected, despite the fact that the patient perceives benefit in terms of pain relief. Indeed, as above, data show that in addition to reducing opioid-related risk, pain can improve when patients lower their opioids, which is evidence in and of itself that opioids do not work for chronic pain for those patients.

g. Just as increased prescribing has been the cause of increased consumption and risk,[125] decreasing opioid prescribing decreases opioid consumption and risk. When doctors prescribe fewer opioids, patients consume fewer opioids, without increases in pain. Limiting opioid prescribing is good medicine, because it decreases exposure to a dangerous and potentially lethal drug, without compromising pain treatment, while at the same time reducing the risk of diversion of unused pills to unauthorized users.

i. In a study in which patients were treated with Tylenol/ibuprofen after parathyroid and thyroid surgery, the authors concluded that such patients "need very little, if any, post-operative opioids.… Decreasing the volume of opioid medications prescribed at discharge will decrease waste and reduce potential for addiction."[126]

ii. A case-control cohort study of 1,231 patients undergoing gynecologic oncology surgery, implemented an "ultrarestrictive opioid prescription protocol" (UROPP), resulting in a significant decrease in the number of opioids dispensed during the entire

[123] Darnall BD, Ziadni MS, Stieg RL, Mackey IG, Kao MC, Flood P. Patient-centered prescription opioid tapering in community outpatients with chronic pain. JAMA Intern Med. 2018. doi:10.1001/jamainternmed.2017.8709, at p. 708.

[124] Gomes T, Mamdani MM, Dhalla I a, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. Arch Intern Med. 2011;171(7):686-691. doi:10.1001/archinternmed.2011.117, at p. 686. See also Lembke *et al.*, Weighing The Risks," fn 3, above, at p. 982; Edlund *et al.*, Role of Opioid Prescription," fn 25, above, at p. 7; Chou *et al.*, "Effectiveness and Risks," fn 60, above, at p. ES-1.

[125] Howard R, Fry B, Gunaseelan V, *et al.* Association of Opioid Prescribing with Opioid Consumption after Surgery in Michigan. JAMA Surgery. 2018, at p. E6.

[126] Shindo M, Lim J, Leon E, Moneta L, Li R, Quintinalla-Diek L. Opioid Prescribing Practice and Needs in Thyroid and Parathyroid Surgery. JAMA Otolaryngology - Head and Neck Surgery. 2018, at p. 1102.

perioperative period, without changes in postoperative pain scores, complications, or increases in the number of refill requests.[127]

A. The authors write, "For patients who underwent laparoscopic or robotic surgery, the mean (SD standard deviation) number of opioid tablets given at discharge was 38.4 (17.4) before implementation of the UROPP and 1.3 (3.7) after implementation (P < .001). After ambulatory surgery, the mean (SD) number of opioid tablets given at discharge was 13.9 (16.6) before implementation of the UROPP and 0.2 (2.1) after implementation (P < .001). The mean (SD) perioperative oral morphine equivalent dose was reduced to 64.3 (207.2) mg from 339.4 (674.4) mg the year prior for all opioid-naive patients (P < .001)."[128]

B. "The significant reduction in the number of dispensed opioids was not associated with an increase in the number of refill requests (104 patients [16.6%] in the pre-UROPP group vs 100 patients [16.5%] in the post-UROPP group; P = .99), the mean (SD) postoperative visit pain scores (1.1 [2.2] for the post-UROPP group vs 1.4 [2.3] for pre-UROPP group; P = .06), or the number of complications (29 cases [4.8%] in the post-UROPP group vs 42 cases [6.7%] in the pre-UROPP group; P = .15)."[129]

h. In sum, the evidence for long-term opioid therapy for chronic non-cancer pain, going all the way back to Portenoy's 1986 article,[130] was never more than "weak." Such "weak evidence" was never sufficient to justify the aggressive promotion and resulting exponential increase in opioid prescribing for chronic pain. Moreover, the "weak evidence" based on flawed studies of the past has been refuted by strong, gold-standard randomized clinical trial evidence[131] that opioids are *not* more effective than non-opioid pain relievers, while imposing greater risk.[132] "Weak evidence" of benefit to a small minority of patients was never sufficient to offset the strong evidence of risk. Finally, and confirming the consensus of independent scientists, according to the National Academy of Science, Engineering, and Medicine (NASEM) 2017 Report, "Pain Management

[127] Mark J, Argentieri DM, Gutierrez CA, *et al.* Ultrarestrictive Opioid Prescription Protocol for Pain Management After Gynecologic and Abdominal Surgery. JAMA Netw Open. 2018;1(8):e185452. doi:10.1001/jamanetworkopen.2018.5452.
[128] *Id.* at p. 1.
[129] *Id.* at pp. 1-2.
[130] Portenoy RK, Foley KM. Chronic use of opioid analgesics in non-malignant pain: report of 38 Cases. Pain. 1986;25(2):171-186.
[131] Krebs *et al.*, "Effect of Opioid," fn 108, above, at p. 873; Welsch *et al.*, "Opioids in Noncancer Pain," fn 114, above, at p. 3.
[132] Krebs *et al.*, "Effect of Opioid," fn 108, above, at p. 880.

and the Opioid Epidemic," there is a "*lack of evidence that the drugs are effective for long-term pain management* (VonKorff *et al.* , 2011)."[133] (Emphasis added).

5. The Pharmaceutical Opioid Industry encouraged and promoted several misconceptions concerning opioid use, including making inaccurate understatements of the risks of addiction to opioids. Even when being prescribed by a doctor for a legitimate pain condition, opioid painkillers are as addictive as heroin purchased on a street corner, because the prescription opioids have the same addictive effects on the neurocircuitry of the brain. There is not, and has never been, scientific support for the claim that the risk of addiction from chronic opioid therapy is low, "rare," or "less than 1%." In fact, the best evidence available shows that the risk of addiction in patients taking opioids for chronic pain is between 10% and 40%. In teens and young adults, the evidence shows that even very limited exposure to prescription opioids can result in addiction. So-called "abuse-deterrent formulations" do not lower the risk of addiction among patients taking them as prescribed.

a. One of the biggest risk factors for becoming addicted to a substance is simple exposure to that substance. The current opioid epidemic is the most tragic and compelling example of that fact in modern history. As opioid prescribing has increased, and opioids have become more accessible to all Americans, opioid use has increased, and with it the rates of opioid addiction. The nearly quadrupling of opioid prescribing between 1999 and 2012 does not merely correlate with rising rates of opioid addiction and related deaths. It is causative. In their 2017 report "Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use," The National Academies of Science, Engineering and Medicine stated, that despite FDA's instruction to the panel that its task was not to assign blame for the current situation, "*certain hypotheses about causes of the epidemic are inescapable.* For example, the data presented earlier in this chapter make a prima facie case that *heavy promotion of opioid prescribing by drug manufacturers (including misleading claims by some)* and substantially increased prescribing by physicians were key contributors to the increase in misuse, OUD, and accompanying harms."[134] (emphasis added)

b. Likewise, decreased exposure to addictive substances decreases risk of addiction. Two natural experiments in the last century tested and proved this hypothesis. The first was Prohibition, a nationwide constitutional ban on the production, importation, transportation, and sale of alcoholic beverages from 1920 to 1933, which led to a sharp decrease in the number

[133] National Academies of Science Engineering and Medicine (NASEM). *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use.*; 2017. doi:10.17226/24781, at p. 29.
[134] *Id.* at pp. 40-41.

of Americans consuming and becoming addicted to alcohol.[135] (There were other unintended consequences of Prohibition, but the positive impact on alcohol consumption and related morbidity is widely under-recognized.) Second, many soldiers in Vietnam during the Vietnam War became addicted to opioids, most of whom stopped using opioids on their return to the United States, where access was limited.[136]

c. There is a clear link between prescription opioid exposure, prescription opioid misuse, and opioid addiction. Opioid misuse, or non-medical use of prescription opioids (NMUPO), is defined as taking an opioid medication other than prescribed. With increased opioid prescribing in the United States, more Americans have been exposed to prescription opioids at higher doses and for longer duration (including those not directly prescribed the opioid), contributing to rising incidence and prevalence of opioid misuse, dependence, and addiction.

i. In 2016, according to the National Survey on Drug Use and Health (NSDUH), more than 11 million Americans misused prescription opioids.[137] More than half obtained the misused prescription opioids from a friend or family member, who in most cases obtained them from a doctor. Thirty-five percent obtained misused prescription opioids directly from a single prescriber. Less than 10% of Americans misusing prescription opioids got them from a 'street dealer.'[138] In other words, a medical prescription is the primary conduit for prescription opioid misuse. It should be noted that NSDUH data, by definition, are based on "households" and, as such, the data do not take into account misuse among homeless or incarcerated populations.

ii. The scientific literature shows that most lifetime nonmedical users of prescription opioids reported a lifetime history of medical use of prescription opioids, that is, most nonmedical users had current or previous legitimate prescriptions. "After controlling for other factors (e.g., gender, race, etc.) we observed an eight-fold increase (OR = 8.1, $p < 0.001$) in lifetime nonmedical use and a 10-fold increase (OR = 9.8, $p < 0.001$) in past year nonmedical use among

[135] Hall W. What are the policy lessons of National Alcohol Prohibition in the United States, 1920-1933? *Addiction*. 2010. doi:10.1111/j.1360-0443.2010.02926.x, at p. 105.
[136] Robins LN, Davis DH, Nurco DN. How permanent was Vietnam drug addiction? *Am J Public Health*. 1974;64(12 Sup):38-43. doi:10.2105/AJPH.64.12_Suppl.38, at p. 40.
[137] Center for Behavioral Health Statistics and Quality. (2017). 2016 National Survey on Drug Use and Health: Detailed Tables. Substance Abuse and Mental Health Services Administration, Rockville, MD, at Table 1.97A.
[138] *Id.* at Table 6.53B.

students who had either current or previous prescriptions for pain medication."[139]

iii. Teens are especially vulnerable to opioid misuse. In 2012, some 1.9 million individuals aged 12 or older misused a prescription drug for the first time within the past twelve months,[140] an average of 1,350 initiatives per day. Prescription drugs now rank fourth among the most-misused substances in America, behind alcohol, tobacco, and marijuana. They rank second among teens. Among teens who became addicted to any drug in the previous year, a quarter started out using a prescription medication: 17 percent began with opioid pain relievers, 5 percent with sedative-hypnotics, and 4 percent with stimulants.

iv. McCabe *et al.* conducted a prospective national study of high school seniors in the U.S. to identify the sequence of medical versus non-medical use of prescription opioids, and the later development of a substance use disorder (addiction). They found that almost one in every two high school seniors who reported the medical use of prescription opioids after initiating NMUPO had two or more substance use disorder (addiction) symptoms at age 35.[141]

A. These data show that teens who are exposed to prescription opioids without a prescription, will often be further exposed through a subsequent medical prescription, and as a result are at increased risk of developing an opioid addiction later in life. The cumulative effect of prescription opioid exposure, through both medical and non-medical use, causally leads to opioid addiction.[142]

B. The authors write, "These results indicate substantial risk for developing SUD among adolescents who have already initiated NMUPO and reinforce the critical role of screening when prescribing opioid analgesics to adolescents."[143] While the authors suggest that screening can play a role in mitigating future opioid addiction,

[139] Boyd CJ, Esteban McCabe S, Teter CJ. Medical and nonmedical use of prescription pain medication by youth in a Detroit-area public school district. Drug Alcohol Depend. 2006. doi:10.1016/j.drugalcdep.2005.05.017, at p. 7.
[140] Substance Abuse and Mental Health Services Administration. Results from the 2012 National Survey on Drug Use and Health: Summary of National Findings. Rockville, MD; 2013., at p. 53.
[141] McCabe SE, Veliz PT, Boyd CJ, Schepis TS, McCabe V V., Schulenberg JE. A prospective study of nonmedical use of prescription opioids during adolescence and subsequent substance use disorder symptoms in early midlife. *Drug Alcohol Depend*. 2019. doi:10.1016/j.drugalcdep.2018.10.027, at p. 379.
[142] *Id.* at p. 381.
[143] *Id.* at p. 383.

screening tools have been shown to have limited efficacy in identifying at risk patients.[144] The more significant goal is to reduce unnecessary and excessive opioid prescribing, which increases risk by increasing exposure to both medical and subsequent non-medical use.

d. Even very limited exposure can result in addiction. A recent study of 14,888 persons aged 16 to 25 years-old who received an initial opioid prescription from a dentist, found that 6% were diagnosed with an opioid use disorder (OUD) within one year. For women in this group, the rate was 10%.[145] This study highlights the risk to teens and young adults, even after limited exposure to a dental procedure, such as removal of wisdom teeth.

e. There are dozens of articles in the scientific literature that provide data on the risk of addiction, dependence, and/or misuse of prescription opioids in the course of medical treatment. In my opinion, these sources, individually and collectively, likely provide a significant underestimation of the true risk of misuse, dependence, and addiction for several reasons:

i. Many studies, particularly trials conducted by opioid manufacturers, screen out patients at higher risk of addiction, who are not commonly screened from real world clinical exposure.

ii. Many studies are not designed *a priori* to identify addiction outcomes, which means that they lack methodology to diagnose or otherwise accurately account for the cases.

iii. Many studies are sponsored and/or written by industry authors, raising conflict of interest and bias issues.

iv. Many studies are too short to assess addiction risk.

A. The natural history of addiction is that it takes some time to develop. Many people who become addicted start out using that substance to solve a problem, from anxiety to insomnia to physical pain. Over time, they become addicted to that substance. Although some become addicted very quickly, most become addicted over months to years, rather than days to weeks.

[144] Clark MR, Hurley RW, Adams MCB. Re-assessing the Validity of the Opioid Risk Tool in a Tertiary Academic Pain Management Center Population. Pain Med. 2018;19(7):1382-1395. http://dx.doi.org/10.1093/pm/pnx332, at p. 1382.

[145] Schroeder AR, Dehghan M, Newman TB, Bentley JP, Park KT. Association of Opioid Prescriptions From Dental Clinicians for US Adolescents and Young Adults With Subsequent Opioid Use and Abuse. JAMA Intern Med. 2018, at p. E6.

B. Risk of addiction to opioids increases with dose and duration of an opioid prescription. The higher the dose, and the longer patients are on them, the more likely they are to misuse opioids and become addicted. As previously stated, for low dose (1-36 MMEs per day) chronic exposure to prescribed opioids (*i.e.*, longer than 90 days), the odds ratio of developing OUD compared to those not prescribed opioids was 14.92 (95% CI = 10.38, 21.46); for medium dose (36-120 MMEs per day) chronic exposure to prescribed opioids, the odds ratio of developing OUD was 28.69 (95% CI = 20.02, 41.13); for high dose (> 120 MMEs per day) chronic exposure to prescribed opioids, the odds ratio of developing OUD was 122.45 (95% CI = 72.79, 205.99).[146] Because of the extraordinary increased risk of OUD with longer exposure, short-term studies are particularly ill-suited to assess that risk accurately.

C. Naliboff et al, in their two-arm, randomized, pragmatic clinical trial comparing stable dose to escalating dose of opioid medications among 135 patients at a VA clinic in Los Angeles, "carefully selected" as appropriate candidates for chronic opioid therapy, nevertheless discharged 27% of patients over the course of the study due to opioid misuse/noncompliance.[147] Urine toxicology screens were included in the protocol.[148] The authors concluded, "Overall, this study confirms that even in carefully selected tertiary-care patients, substance misuse is a significant problem. Importantly, *40% of these misuse problems did not become apparent within the first 6 months, pointing out the need for studies of longer duration*."[149] (emphasis added)

v. Many studies do not use rigorous detection methods

A. Most studies rely solely on patient questionnaire responses to identify problematic behavior, despite generally accepted knowledge that a significant subset of respondents will not disclose behaviors of interest that could subject them to stigma, sanction, or both, as exemplified by the Fleming study (below).

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[146] Edlund *et al.*, "Role of Opioid Prescription," n 25, above, at pp. 559-560.
[147] Naliboff BD, Wu SM, Schieffer B, *et al.* A randomized trial of 2 prescription strategies for opioid treatment of chronic nonmalignant pain. J Pain. 2011;12(2):288-296. doi:10.1016/j.jpain.2010.09.003, at p. 288.
[148] *Id.* at p. 291.
[149] *Id.* at p. 295.

B. A retrospective study of urine toxicology information for 122 patients maintained on chronic opioid therapy, found that 43% of patients had a "problem" with opioids: positive urine toxicology or one or more aberrant drug taking behaviors. The authors concluded "Monitoring both urine toxicology and behavioral issues captured more patients with inappropriate drug-taking behavior than either alone. Requiring a report of behavioral issues and urine toxicology screens for patients receiving chronic opioids creates a more comprehensive monitoring system than either alone."[150]

C. Urine drug tests provide more reliable evidence of drug misuse and addiction than patient report. Fleming found a 24% rate of positive toxicology tests for illicit drugs. "Eighty-four of 185 (46%) patients with positive toxicology testing denied illicit drug use during the research interview, even when they were guaranteed anonymity. This finding confirms clinical observations that patients with chronic pain often mislead their physicians about illicit drug use….Minimization of drug use and drug problems by patients is a major concern in all studies that try to estimate rates of addiction, especially for illegal drugs."[151] In other words, rates of opioid use disorder were potentially 8 times higher in the same population when objective measures of urine drug screens were used.

D. Databases with information on prescribing of controlled substances provide more reliable evidence of drug misuse and addiction than patient report. Checking a database with access to this information gives more reliable evidence on duplicate prescriptions, early refills, 'doctor shopping,' and other indicators of misuse and addiction.[152]

vi. Taking into account these limitations, it is my opinion that a 2015 article by Vowles, *et al.* , nevertheless provides the most reliable pooled estimate of the risk of addiction with chronic opioid

[150] Katz NP, Sherburne S, Beach M, *et al.* Behavioral monitoring and urine toxicology testing in patients receiving long-term opioid therapy. Anesth Analg. 2003. doi:10.1213/01.ANE.0000080159.83342.B5, at p. 1097.

[151] Fleming MF, Balousek SL, Klessig CL, Mundt MP, Brown DD. Substance Use Disorders in a Primary Care Sample Receiving Daily Opioid Therapy. J Pain. 2007. doi:10.1016/j.jpaa.2012.02.008, at pp. 580-581.

[152] https://www.cdc.gov/drugoverdose/pdmp/states.html

therapy.[153] In particular, the Vowles data synthesis prioritized studies using real world data designed to research opioid misuse and addiction. They also prioritized subjects from real world populations, rather than pre-screened clinical trial subjects enrolled in studies not designed to asses misuse or addiction. The authors adopted *a priori* criteria to assess study quality, and then checked their pooled results against the data from the highest quality studies. (By contrast, Fishbain et al, described below, completely excluded studies that did not meet their quality standards, which they admitted were arbitrary.) Further, Vowles, *et al.* disclosed that they had no conflicts of interest. (By contrast, Fishbain was an expert witness for Purdue in at least 3 cases between 2005-2008.[154]) Because most available studies used patient questionnaires rather than objective urine drug screening, Vowles' analysis would represent a likely underestimate of addiction, despite a more appropriate selection of real world populations for the study.

vii. In their systematic review and meta-analysis from 38 studies, Vowles, *et al.* cite a wide range of problematic prescription opioid use in patients being treated for a medical condition, ranging from <1% to 81% across studies.(p. 572) Across most calculations, rates of opioid misuse averaged between 21% and 29% (range, 95% confidence interval [CI]: 13%-38%), and rates of opioid addiction averaged between 8% and 12% (range, 95% CI: 3%-17%).[155]

viii. Even the lower risk classification of 8-12% would be considered a "very common" risk according to the World Health Organization and the Council of International Organizations of Medical Sciences:[156]

A. Very common >= 1/10

B. Common >= 1/100> and < 1/10

C. Uncommon >= 1/1000 and < 1/100

D. Rare >= 1/10,000 and < 1/1,000

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[153] Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, Van Der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: A systematic review and data synthesis. Pain. 2015. doi:10.1097/01.j.pain.0000460357.01998.f1.

[154] Graves v. Purdue Pharma (N.D. Miss. 2008), Rule 26(a)(2) Disclosure of David A. Fishbain, M.D., 8/21/08, at pp. 1-8.

[155] Vowles *et al.*, "Rates of Opioid Misuse," fn 153, above, p. 573.

[156] World Health Organization, CIOMS, http://www.who.int/medicines/areas/quality_safety/safety_efficacy/trainingcourses/definitions.pdf, at p. 10.

E. Very rare < 1/10,000

F. Although the US has not adopted a standard hierarchy like WHO/CIOMS, frequency of adverse events in product information material in the United States is consistent with the WHO standards: "rare" in US labels is commonly < 1/1000; "Infrequent" is >1/1,000 to < 1/100; and anything over 1/100 is "frequent."[157]

ix. Vowles' definition of "misuse" as culled from the included articles is consistent with the DSM-5 definition of mild opioid use disorder. As such, the prevalence of opioid use disorder in Vowles' review using DSM-5 criteria is between 21-29%, including the spectrum from mild through severe OUD. (This is reasonably consistent with the Boscarino, *et al.* study[158] described below.)

x. As with other meta-analyses, reports of misuse/addiction were higher in studies which relied on urine drug testing instead of self-report. For example, included in the Vowles analysis, a study by Brown, *et al.* demonstrated the lower rates based on self-report versus those based on urine toxicology.[159]

A. This was a nonrandomized, open-label study of morphine sulfate ER (Avinza) for a titration period of 2-4 weeks followed by treatment for 12 weeks, administered to patients in primary care settings, evaluated for risk stratification and aberrant behaviors (including urine screening, early renewal requests, increased dose without authorization, oversedation).[160]

B. Only 561 (38%) of the 1,570 originally enrolled patients completed the study, despite its relatively brief duration of 12 weeks of treatment. Of the 890 patients for whom reasons for withdrawal were provided, 410 (46%) included adverse events or failure of treatment among their reasons to withdraw. Five percent were asked to withdraw due to investigator assessment of "high risk level for drug

[157] Eriksson R, Aagaard L, Jensen LJ, *et al.* Discrepancies in listed adverse drug reactions in pharmaceutical product information supplied by the regulatory authorities in Denmark and the USA. Pharmacol Res Perspect. 2014;2(3):1-10. doi:10.1002/prp2.38, at p. 6.
[158] Boscarino J a, Rukstalis MR, Hoffman SN, *et al.* Prevalence of prescription opioid-use disorder among chronic pain patients: comparison of the DSM-5 vs. DSM-4 diagnostic criteria. J Addict Dis. 2011;30(3):185-194. doi:10.1080/10550887.2011.581961.
[159] Brown J, Setnik B, Lee K, *et al.* Assessment , stratification , and monitoring of the risk for prescription opioid misuse and abuse in the primary care setting. 2011;(December). doi:10.5055/jom.2011.0088.
[160] *Id.* at p. 468.

abuse/misuse" after enrollment, and another 5% for "noncompliance."[161]

C. The Vowles analysis incorporates the Brown study's assertion that 2-3% of patients exhibited aberrant drug-related behaviors during visits 2 through 4, and 6% at visit 5, listing those percentages in the "misuse" column.[162]

D. However, Urine Drug Screening (UDS) showed much higher rates of misuse and/or addictive use (although Vowles did not include these findings in his analysis): In particular, 17, 11, 11 and 15 subjects had positive UDS for oxycodone in weeks 2-5, despite prohibition of that drug after Visit 1.[163] By week 5, there were 79 subjects remaining in the study, and the 15 subjects with positive UDS for oxycodone yield a rate of 19% misuse and/or addictive use. This finding provides objective evidence that the prevalence of aberrant drug-related behavior was approximately 3 to 9 times the "2-6%"rate of aberrant drug related behaviors reported by the investigators[164] and cited by Vowles. Such use occurred despite patients having signed agreements to refrain from illicit drug use, and despite knowledge that UDS would be conducted.[165]

E. Objective measures of addictive/aberrant behavior like drug screening results are more reliable than questionnaire responses, and these data from the Brown study support that view.

F. This study was Pfizer-sponsored. Authors included Pfizer/subsidiaries/consultants.[166]

xi. Also included in the Vowles analysis was a study by Fleming, *et al.* , again highlighting the discrepancy between self-report and urine toxicology.[167]

A. This Fleming article reported on substance use disorders among 801 chronic pain patients receiving daily opioid therapy from the same Wisconsin primary care practices that provided the population analyzed in the Fleming article

[161] *Id.* at p. 473.
[162] *Id.* at p. 572.
[163] *Id.* at p. 475, figure 2.
[164] *Id.* at p. 476.
[165] *Id.* at pp. 478-479.
[166] *Id.* at p. 481.
[167] Fleming, *et al.*, "Substance Use Disorders," fn 151, above, at p. 579.

discussed above. Fleming reported a point prevalence of 3.8% for opioid use disorder and 9.7% for substance abuse and/or dependence, using DSM-4 criteria[168] and Vowles incorporated these percentages into the data synthesis.

B. The diagnoses included in the percentages above were based on a 2-hour interview of each patient by the doctor or nurse at the primary care practice.[169] As referenced above, Fleming noted the large disparity between the patients' self-reporting of other drug use and the results of urine drug screening. There were 156 positive urine screens for cannabis compared to 106 self-reports, and 60 positive urine screens for cocaine compared to 24 self-reports.[170]

C. Although the article provided urine drug screen data on certain illicit drugs, sufficient to show the discrepancy between deceptive self-report and objective toxicology, the article did not provide data on the results of urine screens specifically for opioids, so there were no data to determine how many patients had more than expected (evidence of overuse), or opioids that were not prescribed (evidence of overuse), or less/no evidence of the prescribed opioids (evidence of possible diversion).

D. Fleming also reported that "the frequency of opioid use disorders was 4 times higher in patients receiving opioid therapy compared with general population samples (3.8% vs 0.9%)."[171]

E. Despite acknowledging the disparity between toxicology tests and diagnoses based on interview data, Fleming concluded that the "3.8% rate of opioid addiction is a small risk compared with the alternative of continuous pain and suffering. The data presented in this paper support the use of opioids for the treatment of chronic pain by primary care physicians."[172] I disagree with this interpretation of the findings, especially in light of (a) the acknowledged disparity between the urine drug screen rate and the rate based on self-reports; (b) the unreliability of the latter; and (c) the unwarranted assumption that opioid therapy would

[168] *Id.* at p. 573.
[169] *Id.* at p. 574.
[170] *Id.* at p. 579.
[171] Fleming, *et al.*, "Substance Use Disorders," fn 151, above, at p. 573.
[172] *Id.* at p. 581.

alleviate chronic pain and suffering as a trade-off for accepting the risk of dependence or addiction.

f. Boscarino, *et al.* published a study of addiction rates in a large population of patients receiving opioids to treat a medical condition, and found a 41.3% lifetime prevalence of opioid use disorder (using DSM-5 criteria).[173] The research in this study is strengthened by the fact that it was based on a random sample of outpatients seen in a large multispecialty group practice; that drug-use disorder was assessed based on the final DSM-5 criteria; and that subjects were identified through drug orders in the electronic health records, not based on patient self-report or treatment record. Weaknesses include the low survey response rate (33%).[174]

i. "Using electronic records from a large US health care system, we identified outpatients receiving five or more prescription orders for opioid therapy in the past 12 months for noncancer pain (mean prescription orders =10.72; standard deviation =4.96). In 2008, we completed diagnostic interviews with 705 of these patients using the DSM-4 criteria. In the current study, we reassessed these results using the final DSM-5 criteria. Results: The lifetime prevalence of DSM-5 opioid-use disorders using the final DSM-5 criteria was 58.7% for no or few symptoms (2), 28.1% for mild symptoms (2–3), 9.7% for moderate symptoms (4–5), and 3.5% for severe symptoms (six or more). Thus, the lifetime prevalence of "any" prescription opioid-use disorder in this cohort was 41.3% (95% confidence interval [CI] =37.6–45.0)."[175]

ii. "A comparison to the DSM-4 criteria indicated that the majority of patients with lifetime DSM-4 opioid dependence were now classified as having mild opioid-use disorder, based on the DSM-5 criteria (53.6%; 95% CI =44.1–62.8). In ordinal logistic regression predicting no/few, mild, moderate, and severe opioid-use disorder, the best predictors were age 65 years, current pain impairment, trouble sleeping, suicidal thoughts, anxiety disorders, illicit drug use, and history of substance abuse treatment."[176]

iii. In my opinion, the moderate-severe categories of DSM-5 OUD are consistent with Vowles' definitions of addiction, and the milder DSM-5 diagnoses are more consistent with Vowles' definition of

[173] Boscarino J, Hoffman S, Han J. Opioid-use disorder among patients on long-term opioid therapy: impact of final DSM-5 diagnostic criteria on prevalence and correlates. Subst Abuse Rehabil. 2015:83. doi:10.2147/SAR.S85667, at p. 83.
[174] *Id.* at p. 86.
[175] *Id.* at p. 83.
[176] *Id.* at p. 83.

misuse. Accordingly, the totals of 13% "moderate to severe opioid use disorder" in Boscarino are consistent with Vowles' findings of 8-12% "addicted"; further, Vowles' finding of 21-29% "misuse" is reasonably consistent with Boscarino's report of 28% with "mild opioid use disorder." In other words, both of these publications are reasonably consistent in assessing the risk of opioid addiction, ranging from mild to severe, in a clinical population of patients receiving opioids.

g. The 2008 review by Fishbain claimed that the risk of addiction from chronic use of prescription opioids is 3.27% overall; 0.19% if considering de novo opioid users only.[177] Overall, Fishbain included 67 studies in his review and analysis of various measures of addiction or abuse. With respect to the 3.27% / 0.19% addiction rates, Fishbain stated that he relied on a subset of 24 studies with a total of 82 addiction cases among 2,507 patients, identified in Appendix 1 to the article, accessed at the journal website. However, review of the Appendix 1 table shows only 23 studies with 81 addiction cases among 2173 patients, resulting in a prevalence of 3.73%, rather than 3.27%. These figures are not reliable indicators of true prevalence of OUD, for the reasons explained below.

i. The Fishbain analysis included studies that (a) were too short to accurately assess addiction risk; (b) administered low doses; (c) screened out patients at higher risk of addiction; (d) were not designed to identify addiction (e) did not apply rigorous detection methods; and (f) were sponsored and/or written by industry authors, raising conflict of interest and bias issues.

ii. Fishbain's pooled analysis found substantially higher evidence of drug misuse/addiction (14.5%) when findings were based on the more objective measure of aberrant urine toxicology screens.[178]

iii. Fishbain's 2008 review omitted two studies from his 1992 review that had reported substantially higher prevalence than the pooled figure of 3.27% stated in the 2008 article. Studies by Evans, Anesthesia 1981; 36:597-602,[179] (reported 16% addiction in Fishbain's 1992 article[180]), and Katon, Am J Psychiatry 1985;

[177] Fishbain DA, Cole B, Lewis J, Rosomoff HL, Rosomoff RS. What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant drug-related behaviors? a structured evidence-based review. Pain Med. 2008;9(4):444-459. doi:10.1111/j.1526-4637.2007.00370.x, at p. 444.

[178] *Id.* at p. 450.

[179] Evans PJD. Narcotic addiction in patients with chronic pain. Anaesthesia. 1981;36(6):597-602. doi:10.1111/j.1365-2044.1981.tb10323.x.

[180] The Evans article states that the addiction rate was 7%, which appears to be based on 9 cases among the full study population of 130 subjects. (Evans at p. 600) Fishbain's 1992 article states, "Of 56 chronic *benign* patients, 9 or 16% exhibited features of addiction." (Fishbain 1992, Table 4, at 83; emphasis

142:1156-60, (reporting 18.9% addiction)[181], both appeared in Fishbain 1992 but were omitted from Fishbain 2008. Further, the Evans study, in turn, cited to an article by Maruta, Mayo Clinic Proceedings 1976; 54:241-4, [182] which reported an incidence of 24% addiction among a chronic pain population.[183] Fishbain 2008 stated that his search for relevant articles went back to 1966, so these three references would have been within the time period he searched. Fishbain was a litigation consultant for Defendant Purdue between at least 2005-2008, a relationship that was not disclosed in the 2008 article, and which casts the exclusion of the higher prevalence studies in a disturbing light.

iv. Fishbain made an admittedly "arbitrary" decision to apply a 65% "quality score" requirement, despite his own reference to a source stating that studies with scores below 50% are generally not used.[184] The Tables in the Appendix to the Fishbain 2008 article provide the quality scores only for the studies that were included, but not for those that were excluded, so it cannot be determined whether the three higher prevalence studies were excluded for failure to meet the arbitrary quality score threshold, or for other reasons. Their absence from the 2008 review casts further doubt on its reliability.

v. A study reviewed by Fishbain (Passik SD, Kirsh KL, Whitcomb L, *et al.* Monitoring outcomes during long-term opioid therapy for noncancer pain: Results with the pain assessment and documentation tool. J Opioid Manage 2005; 1:5.), was co-authored by Portenoy.[185] In this study, 27 physicians who attended training sessions to serve on "a pain-oriented speakers' bureau" applied a "Pain Assessment and Documentation Tool" (PADT) to 388 of their patients, with diverse pain syndromes, who had been on various regimens of chronic opioid therapy for at least 3 months.[186] The physicians reported their assessment that 5.93% (23/388) of

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added). Thus, comparing the two articles, it appears that Evans included the 74 cancer patients, who had no reported cases of addictive behavior, in the total of 130 subjects. Conversely, Fishbain's 1992 study explicitly studied "Drug Abuse, Dependence, and Addiction in *Chronic Pain Patients*," (emphasis added); thus the figure of 16% (9/56) appears accurate.

[181] Egan K, Katon W. Chronic Pain: Lifetime Psychiatric Diagnoses and Family History. Am J Psychiatry. 1985;(October):1156-1160, at p. 1157.

[182] Note that the Maruta article was actually published in 1979, and the cite in the Evans article lists the incorrect year of publication.

[183] Maruta T., Swanson D., Finlayson, R. Drug Abuse and Dependence in Patients with Chronic Pain. Mayo Clin. Proc. 1979 (April):241-244, at p. 242.

[184] Fishbain, *et al.*, "What Percentage," fn. 177, above, at p. 448.

[185] Passik SD, Kirsh KL, Whitcomb L, *et al.* Monitoring outcomes during long-term opioid therapy for noncancer pain: Results with the Pain Assessment and Documentation Tool. J Opioid Manag. 2005.

[186] *Id.* at p. 258.

their patients were addicted.[187] However, the doctors also reported that 19.3 % (75/388) engaged in 3 or more "aberrant drug-taking behaviors," such as requests for early renewals, increasing doses without authorization, reporting lost or stolen prescriptions, obtaining medications from other doctors, declining physical/social/psychological function, over-sedation, etc.; and that 10.8% (41/388) engaged in 5 or more such behaviors.[188] Their conclusion of 5.93% addicted lacks validity for several reasons.

A. Appendix 1 states: "Of the total sample 5.93% were thought to demonstrate opioid prescription abuse/ addition [sic]."[189] This is not correct, since the 5.93% applies solely to addiction, whereas the abuse rates were much higher, as described above.

B. Other studies on Fishbain's reference lists would count such behaviors as evidence of addiction, such that the addiction rate in the Passik study would be about 2 to 4 times greater than the 5.93% rate based on the doctors' reports. Including the full range of opioid use disorder (mild, moderate, severe) based on DSM-5 criteria, this study's summative results (5.93% + 19.3% +10.8%) demonstrate that 36.06% of patients met DSM-5 criteria for opioid use disorder, approximating the 40% rate of opioid use disorder consistent with the Boscarino, *et al.* study[190] described above.)

C. The possibility of underestimating addiction rate is of particular concern in light of the participating physicians' roles as Speakers' Bureau trainees.

vi. In another study reviewed by Fishbain et al, 10 patients, who had been treated for chronic noncancer pain (CNCP) with morphine for an average of 2 years, participated in a study alternating between one 60 hour period of morphine and one 60 hour period of placebo (Two and a half days each).[191] "When asked 'Do you have any drug craving?' (graded as mild, moderate or severe), no patients reported craving for morphine or a compulsion to take any," during

[187] *Id.* at p. 263.
[188] *Id.* at pp. 260-261.
[189] *Id.* at Appendix I, p. 47.
[190] Boscarino, *et al.*, "Opioid-use disorder," fn 173, above, at p. 83.
[191] Cowan DT, Wilson-Barnett DJ, Griffiths P, Vaughan DJA, Gondhia A, Allan LG. A randomized, double-blind, placebo-controlled, cross-over pilot study to assess the effects of long-term opioid drug consumption and subsequent abstinence in chronic noncancer pain patients receiving controlled-release morphine. Pain Med. 2005. doi:10.1111/j.1526-4637.2005.05020.x, at p. 113.

the period of cessation of opioids.[192] Authors concluded from these data "that there exists a group of CNCP patients whose long-term opioid consumption can be beneficial and remain moderate without them suffering from the consequences of problematic opioid drug use."[193] Appendix 1 states: "0% demonstrated psychological dependence."[194] This conclusion lacks validity for several reasons.

A. The short duration without opioids is insufficient to assess the presence of addiction. Addiction is a chronic relapsing and remitting illness evidenced by a pattern of behavior over weeks to months, not hours to days.

B. Craving and withdrawal are very subjective and not diagnostic of addiction. Further, asking study subjects about "craving" is likely to bias their response: 'craving' is a loaded term associated with addiction. Patients would be savvy enough to want to avoid this pejorative label.

C. This British study was funded by Janssen-Cilag, introducing inherent bias.[195]

D. Although this is a small study that would have little overall impact on the pooled analysis, it is worth attention if only to demonstrate the contradiction between Fishbain's inclusion of an almost absurdly brief study of 60 hours of exposure – not even enough time to develop dependence, let alone addiction—while omitting relevant studies with higher prevalence that he personally cited in his earlier review article.

h. Higgins, *et al.* performed a meta-analysis of incidence of addiction studies, that is, addiction diagnosed in a pre-specified period of time following the initial exposure to a prescription opioid. The authors argued for a 4.7% overall incidence of iatrogenic addiction to prescription opioids,[196] but their findings need to be considered in light of a number of limitations.

i. Incidence will inevitably under-report the number of cases in a population, because it will only examine data for a fixed beginning and endpoint; whereas prevalence is the more accurate marker of

[192] *Id.* at p. 116.
[193] *Id.* at p. 119.
[194] *Id.* at Appendix 1.
[195] *Id.* at p. 113.
[196] Higgins C, Smith BH, Matthews K. Incidence of iatrogenic opioid dependence or abuse in patients with pain who were exposed to opioid analgesic therapy: a systematic review and meta-analysis. Br J Anaesth. 2018;120(6):1335-1344. doi:10.1016/j.bja.2018.03.009, p. 1339.

the number of cases existing in a population at a given point in time, including all cases of addiction among the population taking prescription opioids.

ii. New onset opioid use disorder (incidence) does not take into account the harm done to patients who maintain or relapse to opioid addiction as a result of medical exposure to opioids. That is, continued exposure imposes continued risk of misuse, dependence, overdose, and the panoply of ill effects of chronic opioid therapy described herein.

iii. The authors claimed that the pooled rate was higher for the studies of "weak" opioids than for "strong" opioids because the subjects might have displayed "pseudoaddiction,"[197] i.e., because the opioids were weak, they displayed drug-seeking behaviors to alleviate their pain that were misconstrued by the physicians, rather than because of a use disorder. The report of a higher rate with lower doses is an unreliable, outlier finding that contradicts numerous large, well-done studies demonstrating the dose-response relationship between higher opioid dose and more bad outcomes.

iv. The authors' restrictive criteria resulted in only 12 studies having been included[198] compared to others (e.g., Vowles), who included 38 studies.

v. The authors erroneously stated that Vowles reached a similar conclusion as to the rates of addiction (4.3 v. 4.7%),(p. 1342) when in fact Vowles reported rates of addiction as 8-12%,[199] or approximately 21-29% when the spectrum of mild through severe OUD is included.

vi. Two of three authors report pharma consulting, including Pfizer.[200]

i. The 2010 Cochrane Review by Noble *et al.* (2010) claimed that opioid addiction occurred in "0.27% of participants in the studies that reported that outcome,"[201] and "… serious adverse events, including iatrogenic opioid addiction, were rare."[202] These findings are specious for the following reasons:

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[197] *Id.* at p. 1343.
[198] *Id.* at p. 1335.
[199] Vowles, *et al.*, "Rates of Opioid Misuse," fn 153, above, at p. 569; McNicol, *et al.*, Cochrane Review 2013, fn 74 at p. 28.
[200] Higgins, *et al.*, "Incidence of Iatrogenic," fn 196, above at p. 1343.
[201] Noble, *et al.*, "Long Term Opioid Management," fn. 61, above, at p. 9.
[202] *Id.* at p. 2.

i. The Cochrane 2010 review analyzed 26 studies with 27 treatment groups that enrolled a total of 4,893 participants. Twenty five of the studies were case series or uncontrolled long-term trial continuations. The other was an RCT comparing two opioids.[203] Only 8 of the 26 included studies provided data on addiction: Allan; Anderson; Hassenbusch; McIlwain; Milligan; Mystakidou; Portenoy; and Zenz.

ii. Only one of these studies (Portenoy, 2007)[204] was *a priori* designed to assess risk of opioid use disorder/addiction. The rest were designed to assess pain efficacy, and addiction risk was an afterthought. Further, none applied rigorous detection methods, or in most cases any detection methods at all to assess opioid misuse or addiction. All of the studies excluded patients with a history of alcohol or substance use disorders. Seven of the eight studies were sponsored and/or written by industry authors, raising conflict of interest and bias issues.

A. Allan *et al.* compared efficacy and safety of transdermal fentanyl and sustained release morphine in opioid naïve patients with chronic low back pain over 13 months.[205] Classification as 'opioid naïve' was based on the patient receiving limited opioids in the 4 weeks prior to the study, with no screening for opioid use prior to 4 weeks.[206] Opioid misuse and addiction did not warrant listing in the Adverse Event "Table 8."[207] In other words, it was not a variable the authors were measuring, as corroborated by the absence of any instrument to assess addiction, despite the use of other survey questionnaires used to track other adverse events. Yet the authors claimed "Addiction was not reported as an adverse event for any participant."[208] The authors further stated "No cases of addiction were reported as an adverse event; this is in line with other studies, which have shown that opioids can be used in chronic noncancer pain without significant risk of abuse. [citing Jamison et al, Spine 1998]."[209] The authors' conclusions are not reliable based on methodology inadequacies to assess for addiction risk.

[203] *Id.* at p. 1.
[204] Portenoy, *et al.*, Long Term Use of Controlled-release Oxycodone for Noncancer Pain: Results of a 3-year Registry Study. Clin. J. Pain 2007; 23: 287-299.
[205] Allan L, Richarz U, Simpson K, Slappendel R. Transdermal Fentanyl Versus Sustained Release Oral Morphine in Strong-Opioid Naıve Patients With Chronic Low Back Pain. 2005;30(22):2484-2490, at p. 2484.
[206] *Id.* at p. 2485.
[207] *Id.* at p. 2488.
[208] *Id.*
[209] *Id.* at p 2489.

Even when investigators are attempting to detect addiction and abuse, as in the studies described above, the difficulties are daunting, as indicated by reports of patient concealment of problem behaviors and substantial disparities between questionnaire responses and urine drug screening; when researchers do not look for addiction and abuse, they are quite unlikely to find such evidence. Further, the study was underwritten by Janssen pharmaceuticals, the makers of Duragesic, transdermal fentanyl, suggesting bias conferred by industry sponsorship.[210]

B. Anderson *et al.* followed 30 patients prospectively for 24 months to assess the long-term safety and efficacy of chronic intrathecal morphine (injected into the spinal canal, or into the subarachnoid space so that it reaches the cerebrospinal fluid) in the treatment of chronic pain.[211] Patients with "psychopathological or substance abuse problems" were screened out and deemed ineligible. Questionnaires were used to track many different variables, but none asked about signs and symptoms of opioid use disorder. The authors report that one patient (1/30, 3%) "was withdrawn from therapy because of drug-seeking behavior …. "[212] This patient "complained of continually escalating pain after infusion system implant, despite successful pain relief during trial at an epidural dose of less than 10mg per day … and sought to obtain oral narcotics from other health care providers," although the authors do not disclose how they obtained this information. When further requests for dose increases were denied, the patient dropped out of the study.[213] The authors conclude "In general, the incidence of addiction among patients with nonmalignant pain receiving chronic opioid is low," but their findings are unreliable given methodological failures to assess addiction risk. The study was sponsored by Medtronics, Inc., the makers of the intrathecal pump.[214]

C. Hassenbusch, like Anderson, examined a case series of patients (22) with intrathecal opioid infusion pumps. In this

[210] *Id.* at p. 2484.
[211] Anderson VC, Ph D, Burchiel KJ. Prospective Study of Long-term Intrathecal Morphine in the Management of Chronic Nonmalignant Pain. 1999;44(2), at p. 289.
[212] *Id.* at p. 292.
[213] *Id.* at pp. 295-296.
[214] *Id.* at p. 299.

case, they followed patients for 5 years.[215] The same limitations described in the Anderson study apply here: patients with history of mental illness or addiction were excluded,[216] and there were no screening instruments or any other detection method to assess for opioid misuse or addiction. Yet the authors conclude "There was no occurrence of opioid dependence, either physical or psychological…."[217]

D. McIlwain *et al.* did a 52-week open label extension study of oxymorphone extended release (ER) in patients with moderate to severe chronic osteoarthritis related pain.[218] The study was sponsored by Endo Pharmaceuticals, the makers of the study drug.[219] The study did not use screening instruments or other detection methods for opioid misuse or addiction. Their Table 2 of adverse events did not include opioid misuse/addiction, despite including 11 other opioid-related adverse events.[220] Despite the absence of any method for detecting or measuring addiction risk, the authors concluded, "No instances of drug addiction or abuse were recorded."[221]

E. Milligan *et al.* studied 532 chronic noncancer pain patients (only 301 completed the trial) being treated with transdermal fentanyl for up to 12 months. They report "drug abuse/dependence" in less than 1% of their sample, but qualify this by saying, "none was considered definitely related to the treatment."[222] Like the other studies included in the addiction risk assessment of the 2010 Cochrane review, this study was not designed to reliably assess addiction risk: patients with a history of substance abuse or psychiatric disorders were excluded, no screening or detection instruments for opioid misuse or addiction were

[215] Hassenbusch, S, Stanton-Hicks, M, Covington, *et al.* Long Term Intraspinal Infusions Of Opioids in the Treatment of Neuropathic Pain. Journal of Pain and Symptom Management. 1995:10:527-543, at p. 529.
[216] *Id.* at p. 528.
[217] *Id.* at p. 536.
[218] McIlwain H, Ahdieh H. Safety , Tolerability , and Effectiveness of Oxymorphone Extended Release for Moderate to Severe Osteoarthritis Pain A One-Year Study. Am J Ther. 2005;112:106-112, p. 106.
[219] *Id.* at p. 111.
[220] *Id.* at p. 108.
[221] *Id.* at p 109.
[222] Milligan K, Lanteri-minet M, Borchert K, *et al.* Evaluation of Long-term Efficacy and Safety of Transdermal Fentanyl in the Treatment of Chronic Noncancer Pain. 2001;2(4):197-204. doi:10.1054/jpai.2001.25352, at p. 197.

described.[223] The authors report three cases of "drug abuse (2 moderate and 1 severe)"; two cases of "moderate physical drug dependence (as opposed to abuse)"; and "no reports of addiction."[224] Yet how these concepts were defined and the cases detected are not clarified. The study was supported by a grant from Janssen.[225] Despite these serious flaws, the authors concluded, "There were no reports of addictive behavior in any of the patients during this long-term study. Because the fear of addiction is one of the reasons for the underuse of opioids in chronic noncancer pain, this study provides further evidence that these fears are unfounded."[226] This conclusion does not follow from the evidence.

F. The study by Mystakidou recruited 529 patients into an open-label study of transdermal therapeutic system-fentanyl (TTS-F) for 28 days, followed by an open-label follow-up for a median of 10 months between 1996-2002.[227] The first page of the article includes the copyright symbol for the American Pain Society, which had been funded substantially by opioid manufacturers; the authors do not disclose a corporate sponsor, but they cite to prior studies of Dellemijn and Allan that acknowledged participation by Janssen-Cilag, the manufacturer of Duragesic TTS-F, and the Janssen Research Foundation.[228] A complete description of exclusion criteria was not provided; the authors stated only, "Exclusion criteria included a history of opioid abuse, surgery in the preceding 7 days or scheduled surgery, contraindications to opioids, and opioids use outside of the designated treatment regimen."[229] No information is provided as to what constituted "contraindications to opioids;" and the exclusion for "opioids use outside the designated treatment regimen" inherently eliminates the population with the most obvious defining characteristic of addiction. The authors state, "Following discontinuation from the study, no patient complained of withdrawal symptoms or was

[223] *Id.* at p. 198.
[224] *Id.* at pp. 201-202.
[225] *Id.* at p. 197.
[226] *Id.* at p. 203.
[227] Mystakidou, Kyriaki, Parpa, Efi, Tsilika, Eleni, Mavromati A, Smyrniotis V, Georgaki, Stavroula, Vlahos L. Long-Term Management of Noncancer Pain With Transdermal Therapeutic System-Fentanyl. *J Pain*. 2003;4(6):298-306. doi:10.1016/S1526-5900(03)00632-1, at pp. 298-299.
[228] *Id.* at p. 305.
[229] *Id.* at p. 299

found to display dependency"[230]; however, like the others described above, the Mystakidou study included no protocol to detect addiction, withdrawal, dependency or abuse, either during the study or after discontinuation. Without such information, it is unknown whether patients experienced such effects during the study, nor whether they returned to their former opioid regimens after the study ended.

G. Portenoy describes an open label continuation study using controlled release (CR) oxycodone (Oxycontin) in a population of chronic pain patients who had previously participated in controlled trials of CR oxycodone for pain. Unlike the other studies included in the 2010 Cochrane review, this study by Portenoy *et al.* included specific methods for assessing opioid misuse and addiction, including an independent review panel to determine types of problematic opioid use. However, the information evaluated by the independent review panel was based entirely on patient self-report, which we know to be inherently unreliable, particularly in the context of a clinical trial designed to assess pain efficacy. The authors reported "6 of 227 (2.6%) patients could be considered to have probable drug abuse or dependence based on the independent expert review, none of whom met diagnostic criteria for substance abuse."[231] This appears to be the basis for the "3%" figure used in the Noble 2010 review. However, the article also reported that 133 patients dropped out of the study, so the use of 227 as the denominator is questionable. Further, "Patients with self-reported past or present substance or alcohol abuse" were excluded, as were patients with a "documented allergy to oxycodone or other opioids."[232] Finally, the study was sponsored by Purdue Pharma, the makers of Oxycontin.[233]

H. Zenz described 100 chronic nonmalignant pain patients who were given opioids in an open-label, non-controlled setting, between 1986-1990.[234] Treatment was discontinued in 59 patients (21 did not respond to opioid therapy; 20 changed to an alternative treatment method; 10 were

[230] *Id.* at pp. 300-301.
[231] Portenoy, *et al.*, "Long Term Use," fn. 204, above, at p. 296.
[232] *Id.* at p. 288.
[233] *Id.* at p. 287.
[234] Zenz, Michael; Strumpf, Michael; Tryba M. Long Term Oral Opioid Therapy in Patients with Chronic Nonmalignant Pain. 1992:69-77, at p. 70.

discontinued for "lack of compliance;" and 8 died during the study period).[235] Zenz reported, "There were no cases of respiratory distress or addiction to opioids."[236] As in the studies described above, Zenz had no protocol to look for or record addiction or abuse. No details were provided as to the type of "noncompliance" that caused 10 patients to be discontinued, but "noncompliance" in the setting of opioid therapy is a red flag for concern over signs of abuse as to which the lack of further information is another conspicuous weakness of the study.

I. In summary, the seven studies contributing to the addiction rate reported in the 2010 Cochrane review are subject to common inadequacies, primary among them their focus on efficacy and from lack of any method to detect addiction or abuse, and the screening out of higher risk patients. Their data do not square with the much higher prevalence of OUD reported among real world chronic pain populations, by investigators who were looking for it.

j. Opioid manufacturers conveyed the misleading message that as long as doctors were prescribing opioids to patients in pain, the prescription pad conferred protection against patients becoming addicted. The false claim of low rates of addiction with prescription opioids when prescribed for pain had a significant impact on the increased likelihood that physicians would prescribe. Defendants successfully encouraged doctors into believing the risks of addiction were low, which directly contributed to increased prescribing, by promoting poor quality evidence highlighting low addiction rates among pain patients. Contrary to what Defendants claimed, opioid painkillers are as addictive as heroin purchased on a street corner, even when being prescribed by a doctor for a legitimate pain condition, because the prescription opioids have the same addictive effects on the neurocircuitry of the brain.

i. As mentioned above, the 1980 New England Journal of Medicine letter to the editor entitled "Addiction Rare in Patients Treated with Narcotics," reported only four cases of addiction among 11,882 patients treated with opioids.[237] This letter did not represent relevant or reliable evidence of the risk of opioids for chronic non-cancer pain, because the article pertained to a hospitalized population, including patients who received no more than a single dose, rather than the outpatient chronic pain population for whom opioid use was promoted and became prevalent.

[235] *Id.* at p. 73.
[236] *Id.* at p. 69.
[237] Porter, Jick, *et al.*, "Addiction Rare," fn. 39, above, at p. 123.

ii. Nonetheless, it was widely cited by doctors and medical organizations and frequently quoted by the pharmaceutical industry in its advertisements for opioids in the treatment of chronic pain, as proving that "less-than-1%" of patients receiving opioids for pain becomes addicted.

iii. Defendants' promotional messages continued to cite their "less-than-1%" claim, or that addiction with chronic opioid therapy was "rare," despite numerous peer-reviewed studies to the contrary over a period of decades. (See Appendix I.)

iv. In 1992, Fishbain had published an earlier study of addiction risk with chronic opioid exposure, which stated, "According to the results of this review, to date, only three studies have attempted to address the concepts of psychological dependence and compulsive use, i.e., addiction, in an acceptable fashion. These studies have found a prevalence from 3.2% to a high of 16% for the possibility of addiction in chronic pain patients".[238] The same article also stated, "It is interesting to note that the only two studies to utilize urine toxicologies found illicit drug use in 6.41 and 12.5% of their chronic pain patients. These results may therefore indirectly support the results of the other 'addiction' studies described earlier, as they are both within the prevalence percentages derived from these studies".[239] However, these higher prevalence figures, and the sources from which they came, were omitted from Fishbain's 2008 analysis.

v. Also, Fishbain's 2008 review[240] included data from a 1992 study by Bouckoms, *et al.* , which found that 14 of 59 clinic patients (24%) taking opioids for long-term met criteria for "narcotics addiction".[241] Bouckoms also stated: "The influence of population sample bias in prevalence studies of narcotic addiction is dramatically shown in a comparison of studies in the literature. Table 5 summarizes data from the studies of Porter, Maruta, Taub, Evans, Langemark, and Portenoy, wherein the prevalence of addiction was 0.03%, 24%, 4.2%, 7%, 35%, and 5%, respectively".[242] Notably, the 0.03% figure in Bouckoms' text is based on the Porter and Jick 1980 Letter[243]—the only one of the 5

[238] Fishbain DA, Rosomoff HL, Rosomoff RS. Drug abuse, dependence, and addiction in chronic pain patients. Clin J Pain. 1992. doi:10.1097/00002508-199206000-00003, at p. 80.
[239] *Id.* at p. 81.
[240] Fishbain, *et al.*, "What Percentage," fn. 177, above.
[241] Bouckoms AJ, Masand P, Murray GB, Cassem EH, Stern TA, Tesar GE. Chronic nonmalignant pain treated with long-term oral narcotic analgesics. Ann Clin Psychiatry. 1992. doi:10.3109/10401239209149570, at p. 185.
[242] *Id.* at p. 188.
[243] Porter, Jick, *et al.*, "Addiction Rare," fn. 39, above, at p. 123.

references that was *not* based on a population of patients treated with opioids for chronic pain.

vi. All of the sources cited by Bouckoms were available to Defendants from 1992 on. Yet their marketing and promotional statements beginning in the 1990s cited the inapt Porter and Jick study[244] of hospitalized patients with any exposure to opioids, regardless of duration, as the source for the claim of "less than one percent" prevalence of addiction. I am not aware of any Defendants having issued a marketing or promotional statement citing the results of 24%, 4.2%, 7%, 35% or 5%, referenced by Bouckoms in 1992.[245] Nor am I aware of any such statements by Defendants that cited the range of "prevalence from 3.2% to a high of 16% for the possibility of addiction" reported by Fishbain in 1992.[246]

vii. Later publications also reported addiction rates that did not appear in the promotional materials that I have reviewed. These include the following prevalence studies cited in the Vowles[247] data synthesis: Manchikanti (2003),[248] Cowan (2003),[249] Adams (2006),[250] Fleming (2007),[251] Banta-Greene (2009),[252] Schneider (2009),[253] Edlund (2007),[254] Hojsted (2010),[255] Jamison (2010),[256]

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[244] *Id.*
[245] Bouckoms, *et al.*, "Chronic Nonmalignant," fn. 241, above, at p. 188.
[246] Fishbain, *et al.*, "Drug Abuse," fn 238, above, at p. 80.
[247] Vowles, *et al.*, "Rates of Opioid Misuse," fn. 153, above.
[248] Manchikanti et.al Prevalence of prescription drug abuse and dependency in patients with chronic pain in western Kentucky. J Ky Med Assoc 2003;101:511–17, at p. 511.
[249] Cowan DT, Wilson-Barnett J, Griffiths P, Allan LG. A survey of chronic noncancer pain patients prescribed opioid analgesics. Pain Med. 2003;4(4):340-351, at p. 340.
[250] Adams EH, Breiner S, Cicero TJ, *et al.* A Comparison of the Abuse Liability of Tramadol, NSAIDs, and Hydrocodone in Patients with Chronic Pain. J Pain Symptom Manage. 2006;31(5):465-476, at p. 465.
[251] Fleming, *et al.*, "Substance Use Disorders," fn. 151, above, at p. 573.
[252] Banta-Green CJ, Merrill JO, Doyle SR, Boudreau DM, Calsyn D a. Opioid use behaviors, mental health and pain--development of a typology of chronic pain patients. *Drug Alcohol Depend*. 2009;104(1-2):34-42, at p. 37.
[253] Schneider, MD, PhD JP, Kirsh, PhD KL. Defining clinical issues around tolerance, hyperalgesia, and addiction: A quantitative and qualitative outcome study of long-term opioid dosing in a chronic pain practice. *J Opioid Manag*. 2010;6(6):385-395, at p. 390.
[254] Edlund MJ, Sullivan M, Steffick D, Harris KM, Wells KB. Do users of regularly prescribed opioids have higher rates of substance use problems than nonusers? *Pain Med*. 2007. doi:10.1111/j.1526-4637.2006.00200.x, at p. 651.
[255] Højsted J, Nielsen PR, Guldstrand SK, Frich L, Sjøgren P. Classification and identification of opioid addiction in chronic pain patients. *Eur J Pain*. 2010;14(10):1014-1020, at p. 1014.
[256] Jamison RN, Butler SF, Budman SH, Edwards RR, Wasan AD. Gender Differences in Risk Factors for Aberrant Prescription Opioid Use. *J Pain*. 2010. doi:10.1016/j.jpain.2009.07.016, at p. 5.

Passik (2011),[257] and Meltzer (2012),[258] which reported addiction at 8.4%, 2.8%, 4.9%, 3.8%, 13%, 15.7%, 0.7%, 14.4-19.3%, 34.1%, 6-11%, and 23%, respectively.

viii. With one exception, all of these studies showed addiction prevalence multiple times higher than the "less than one percent" figure that Defendants continued to cite, while omitting data from these peer-reviewed studies of relevant, real world populations of chronic opioid patients.

ix. The sole exception, the Edlund (2007) study, can be explained in that the 0.7% incidence pertained to the entire healthcare database, rather than the subset of prescription opioid users. As to the latter group, the incidence of addiction was actually 7.3%,[259] which is consistent with the other data synthesized by Vowles. Because this distinction is important and not obvious, I provide the additional details below.

A. First, the data used in the Edlund 2007 study came from a nationally representative community sample, Healthcare for Communities (HCC). The sample consisted of 9,279 people who were interviewed to investigate self-reported opioid misuse and "problem" opioid misuse among users and non-users of prescribed opioids, as well as use/ "problem use" of other substances (illicit drugs other than opioids, alcohol). "Opioid misuse" was defined to mean either without a doctor's prescription, or in a larger amount or for a longer time than prescribed. "Problem opioid use" added criteria of tolerance and/or psychological or emotional problems due to drug use to the general "misuse" definition.[260]

B. This Edlund study did not provide any data on "addiction." Nevertheless, the Vowles data synthesis included a value of 0.7% for "addiction."[261] However, the Edlund definition of "problem opioid use" is consistent with Vowles' definition of "addiction" to mean a "[p]attern of continued use with experience of, or demonstrated potential for, harm, (e.g.,

[257] Passik SD, Messina J, Golsorkhi A, Xie F. Aberrant drug-related behavior observed during clinical studies involving patients taking chronic opioid therapy for persistent pain and fentanyl buccal tablet for breakthrough pain. *J Pain Symptom Manage*. 2011;41(1):116-125, at p. 116.
[258] Meltzer, E, Rybin, D, *et al.* Aberrant Drug-Related Behaviors: Unsystematic Documentation Does Not Identify Prescription Drug Use Disorder. Pain Med. 2012 November; 13(11): 1436-1443, at 1437.
[259] Edlund, *et al.*, "Do Users Have Higher Rates," fn 254, above, at p. 651.
[260] *Id.* at pp. 649-650.
[261] Vowles, *et al.*, "Rates of Opioid Misuse," fn. 153, above, at p. 572, Table 2.

impaired control over drug use, compulsive use, continued use despite harm, and craving)."[262]

C. Further, the reference to "0.7%" in the Edlund 2007 article appearing at p. 651, stated the percentage of problem opioid misuse in "*the total HCC sample*," (emphasis added), which consisted of 8,997 (97%) nonusers of prescription opioids compared to 282 (3%) of the HCC sample who were prescription opioid users. The Edlund study reported, "Rates of problem opioid misuse were *significantly higher in those with prescription opioid use* (7.3%, 17 out of 282, vs. 0.5%, 69 out of 8,997, P<0.001."; emphasis added).[263]

D. In the absence of any data specific to addiction in the Edlund article, it can only be inferred that Vowles intended to use Edlund's "problem opioid misuse" as a surrogate for addiction, and that the reference to 0.7% for the total population is inappropriate, since all of the other studies that Vowles synthesized had determined the percentage of addiction/ misuse among subjects exposed to prescription opioids, and not the percentage of addiction/misuse among a general population consisting almost entirely of non-users of prescription opioids.

E. Thus, the proper figure from the Edlund study to include in the Vowles data synthesis would have been "7.3%, 17 out of 282" prescription opioid users, and the inclusion of the prescription opioid nonusers differentiates the Edlund study from all others that Vowles used in his data synthesis. At 7.3%, the Edlund study is very similar to the range of 8-12% addiction that Vowles assessed for the studies as a whole.

F. Finally, Edlund acknowledged, "Our analyses of substance abuse rely on self-report, which might suffer from recall bias, or respondents might under-report symptoms due to the stigma associated with illicit substance abuse. To the extent this is true, our results are underestimates of the true rates."[264] Accordingly, 7.3% is a lower bound, and the true rate of addiction among the population in the Edlund study may well have been greater.

[262] *Id.* at p. 570.
[263] Edlund, *et al.*, "Do Users Have Higher Rates," fn. 254, at p. 651.
[264] *Id.* at p. 654.

x. Purdue's Power Point presentation dated September 12, 2014, is addressed to a potential business opportunity involving "Project Tango." The document identifies Tango as the "global leader in the pharmaceutical treatment of addiction," and further states, "Addiction treatment is a good fit and natural next step for Purdue," because "Pain treatment and addiction are naturally linked."[265] I agree that pain treatment with opioids is naturally linked with addiction. Furthermore, this linkage would have been known and obvious to Defendants throughout the period of time when they marketed and promoted their opioid medications with the false message that addiction was "less than 1%," or "rare," or "uncommon," and that false message deprived doctors and patients of necessary data to inform the true risks of chronic opioid therapy.

6. The Pharmaceutical Opioid Industry encouraged and promoted several misconceptions concerning opioid use, including making inaccurate claims as to the levels to which doses can be safely increased. With increasing dosage and duration of opioids, the risk of addiction goes up, as do the risks of many other adverse health consequences, including tolerance, dependence, withdrawal, opioid induced hyperalgesia, immunosuppression, severe constipation, depression, cognitive decline, cardiac effects, breathing effects, hormonal effects, accidental overdose, and death. There is an undeniable link between suicide and opioids. Opioids are associated with more adverse medical outcomes and more mortality than non-opioid analgesics (NSAIDS).

a. Through drug reps, key opinion leaders, and CME content, manufacturers of opioids conveyed the misleading message that there is no ceiling dose for opioids. In an article by Portenoy's 1986 co-author Foley and others they wrote "We disagree with the concept of setting a maximum dose. The pharmacology of opioid use in the treatment of pain is based on dose titration to effect."[266] This statement encouraged the practice of increasing the dose of opioids over time as tolerance developed. I have seen scores of patients over the years on very high doses of opioids, some as high as 2,000 morphine milligram equivalents per day (MED). To put that in perspective, the average heroin addicted individual consumes 100 morphine milligram equivalents daily. Meanwhile, there is no evidence to support the use of higher doses of opioids, and mounting evidence that risks of opioids are directly related to dose and duration: the higher the dose, and the longer patients are on them, the higher the risk.[267]

b. A study by Dunn *et al.* found an increased risk of opioid-related overdose death in a step-wise dose response relationship: "Compared with patients receiving 1 to 20 mg/d of opioids (0.2% annual overdose rate), patients

[265] PPLPC016000255303, produced natively at *14 and *8.
[266] Foley KM, Fins JJ, Inturrisi CE. A true believer's flawed analysis. *Arch Intern Med*. 2011. doi:10.1001/archinternmed.2011.166, at p. 867.
[267] Edlund, *et al.*, "Role of Opioid Prescription," fn. 25, above, at p. 557.

receiving 50 to 99 mg/d had a 3.7-fold increase in overdose risk (95% CI, 1.5 to 9.5) and a 0.7% annual overdose rate. Patients receiving 100 mg/d or more had an 8.9-fold increase in overdose risk (CI, 4.0 to 19.7) and a 1.8% annual overdose rate. … Patients receiving higher doses of prescribed opioids are at increased risk for overdose, which underscores the need for close supervision of these patients."[268]

c. Dunn also noted that their study "provides the first estimates that directly link receipt of medically prescribed opioids to overdose risk, and suggests that overdose risk is elevated in patients receiving medically prescribed opioids, particularly in patients receiving higher doses."[269] The study also provided important data on the relationship between fatal and non-fatal overdoses, in particular, that "[m]ore than 7 nonfatal overdoses events occurred for each fatal overdose" in the study cohort.[270]… "The inclusion of nonfatal overdoses improves understanding of the problem, because most previous work has examined only fatal overdoses. The overall overdose rate in the sample was 148 per 100,000 person-years, indicating that fatal overdose represents only the tip of the iceberg (88% of identified overdose events were nonfatal). Most of the nonfatal overdoses were clinically serious."[271] These data mean that on a nationwide basis, the over 14,000 fatal prescription opioid overdoses in 2017 would translate to over 100,000 nonfatal overdoses. While fatal cases justifiably capture our attention, it must also be recognized that the cost of a nonfatal overdose is far greater in terms of medical and community resources, to treat the overdose episode itself, and to provide long-term care for the OUD disease that gave rise to the event.

d. A study by Bohnert *et al.* found an increased risk of opioid-related overdose death at each level of increased dose, and particularly at doses greater than 100 MEDs. Compared to the Reference dose of 1 to < 20 MED, the adjusted hazard ratio for 20 to < 50 MED was 1.88; for 50 to < 100 MED, the hazard ratio was 4.63; and at > 100 MED, the hazard ratio was 7.18; all three results were statistically significant. A similar pattern held for each of three diagnostic groups (substance use disorders, chronic pain, and cancer): "The adjusted hazard ratios (HRs) associated with a maximum prescribed dose of 100 mg/d or more, compared with the dose category 1 mg/d to less than 20 mg/d, were as follows: among those with substance use disorders, adjusted HR = 4.54 (95% confidence interval [CI], 2.46-8.37; absolute risk difference approximation [ARDA] = 0.14%); among those with chronic pain, adjusted HR = 7.18 (95% CI, 4.85-10.65; ARDA = 0.25%); among those with acute pain, adjusted HR =

[268] Dunn KM, Saunders KW, Rutter CM, *et al.* Opioid prescriptions for chronic pain and overdose: A cohort study. *Ann Intern Med*. 2010;152(2):85-92, at p. 85.
[269] *Id.* at p. 90.
[270] *Id.* at p. 89.
[271] *Id.* at p. 91.

6.64 (95% CI, 3.31-13.31; ARDA = 0.23%); and among those with cancer, adjusted HR = 11.99 (95% CI, 4.42-32.56; ARDA = 0.45%)."[109272] Opioid therapy is generally accepted as appropriate for cancer patients, especially in late stages or severe pain. Nevertheless, with the advent of improved cancer therapies, more patients are living longer with disease or remission, and opioid therapy should be implemented with caution, to minimize risk of addiction.

e. A population based nested case control study of 607,156 people prescribed opioids found that an average daily dose of 200 mg or more of morphine or equivalent was associated with a nearly 3-fold, statistically significant increased risk of opioid-related mortality relative to low daily doses (< 20 mg of morphine or equivalent), Odds Ratio (OR) 2.88, 95% CI 1.79-4.63.[273]

f. The risk of addiction, like the risk of overdose and mortality, also increases in a dose-dependent manner. As previously stated, "Clinicians should be aware that as they proceed from acute to chronic opioid therapy, the evidence of efficacy decreases whereas the opioid use disorder (OUD) risk increases substantially."[274] For low dose (1-36 MMEs per day) chronic exposure to prescribed opioids, the odds ratio of developing OUD compared to those not prescribed opioids was 14.92 (95% CI = 10.38, 21.46); for medium dose (36-120 MMEs per day) chronic exposure to prescribed opioids, the odds ratio of developing OUD was 28.69 (95% CI = 20.02, 41.13); for high dose (> 120 MMEs per day) chronic exposure to prescribed opioids, the odds ratio of developing OUD was 122.45 (95% CI = 72.79, 205.99).[275]

g. The link between suicide and opioids is undeniable and complex. In a *New England Journal of Medicine* article on opioids and suicide risk, Bohnert *et al.* note that "A reduction in the quantity of prescribed opioids may function as a 'means restriction' by reducing patients' access to a lethal means of causing an intentional or unintentional opioid overdose. To this end, clinicians should ask about their patients' access to opioids, including past prescriptions and medications prescribed to others in the same home. Taper protocols that involve small decreases in dosage over time are successful for reducing dosages and may actually reduce pain intensity.

[272] Bohnert ASB, Valenstein M, Bair MJ, *et al.* Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA - J Am Med Assoc*. 2011;305(13):1315-1321, at p. 1315; Olsen, *et al.*, Pain relief that matters, fn 107, above.
[273] Gomes *et.al,* "Opioid Dose," fn. 124, above, at p. 686.
[274] Edlund, *et.al.* "Role of Opioid Prescription," fn. 25, above, at p. 561.
[275] *Id.* at pp. 559-560.

However, whether tapering changes the risk of either suicide or overdose is unknown."[276]

h. Opioids are associated with more adverse medical outcomes and increased mortality than non-opioid analgesics (NSAIDS),[277] contrary to the claim that morbidity and mortality of non-opioid medications (NSAIDS) for pain are comparable.[278]

7. The Pharmaceutical Opioid Industry encouraged and promoted several misconceptions concerning opioid use, including mischaracterizing addictive behavior as "pseudoaddiction" and tolerance as "breakthrough pain." There is no such thing as "pseudoaddiction," and no evidence that providing more opioids is an appropriate response to patients exhibiting drug-seeking behavior. On the contrary, tolerance, dependence, and withdrawal, markers of neuroadaptation to the drug, constitute an adverse medical reaction and should trigger consideration of tapering the opioid medication, not increasing its dose.

a. Tolerance is the need for more and more of the drug to get the same effect. As the dose is increased to overcome tolerance to the pain relieving effects of the drug, patients are exposed to the other dose-dependent risks associated with the drugs, including the risk of death. Furthermore, tolerance to the respiratory suppressant effects (the ability of opioids to decrease breathing rate and thus blood oxygenation) develops more slowly than tolerance to the pain-relieving effects of the drug. As such, as the dose of opioids goes up to target pain relief, the breathing rate goes down, increasing the risk of accidental overdose and death.[279] Tolerance is not a short-lived phenomenon. It persists and renders the opioid largely ineffective for the underlying pain condition. Despite tolerance, patients often endorse ongoing subjective benefit from the opioid, not because it is treating underlying pain, but because it is relieving opioid withdrawal from the previous dose.

b. Based on a single case report of a patient who engaged in drug-seeking behavior,[280] doctors were encouraged to conceptualize the patient's addictive behavior as evidence of under-treated pain. This case report was co-authored by David Haddox, who went on to work at Purdue. The

[276] Bohnert ASB, Ilgen MA. Understanding Links among Opioid Use, Overdose, and Suicide. *N Engl J Med*. 2019. doi:10.1056/nejmra1802148, at p. 76

[277] Solomon DH, Rassen J a, Glynn RJ, Lee J, Levin R, Schneeweiss S. The comparative safety of analgesics in older adults with arthritis. Arch Intern Med. 2010;170(22):1968-1976. doi:10.1001/archinternmed.2010.391, at p. 1968.

[278] Tayeb BO, Barreiro AE, Bradshaw YS, Chui KKH, Carr DB. Durations of opioid, nonopioid drug, and behavioral clinical trials for chronic pain: Adequate or inadequate? *Pain Med (United States)*. 2016. doi:10.1093/PM/PNW245, at p. 2043.

[279] Lembke, *et al.*, "Weighing the Risks," fn. 3, above, at p. 987; Chou, *et al.*, "Effectiveness and Risks," fn. 60, above, at p. ES-25.

[280] Weissman DE, Haddox JD. Opioid pseudoaddiction--an iatrogenic syndrome. *Pain*. 1989;36(3):363-366. http://www.ncbi.nlm.nih.gov/pubmed/2710565.

authors of the case report incorrectly asserted that treatment of pain is often inadequate because of "excessive fears of tolerance and dependence by both health professionals and the public,"[281] when in fact those fears were well-justified and should have been respected. In addition, since the conditions of addiction and dependence are common, their recommended treatment to continue administering or even increase opioids despite addictive behavior, undoubtedly put more patients at risk of becoming addicted or dependent.

c. Patients develop tolerance over time to daily opioids, such that the opioid partially or completely stops working to relieve pain. Once tolerance occurs, patients may experience opioid withdrawal multiple times a day between pain pill doses, and need higher and higher doses to avoid between-pill withdrawal. Tolerance, dependence, and withdrawal, markers of neuroadaptation to the drug, constitute an adverse medical reaction and should trigger consideration of tapering the opioid medication. Instead, in the 1990's and early aughts, Defendants' promotional messages advised doctors that drug-seeking behavior should be considered "pseudoaddiction," that should be addressed by increasing opioids or 'rotating' to another opioid to manage tolerance, which in turn led to patients being escalated to higher doses that conferred greater risk. (See Appendix for examples).

d. In a review article on use of the term 'pseudoaddiction,' the authors found, "By 2014, pseudoaddiction was discussed in 224 articles. Only 18 of these articles contributed to or questioned pseudoaddiction from an anecdotal or theoretical standpoint, and none empirically tested or confirmed its existence. Twelve of these articles, including all four that acknowledged pharmaceutical funding, were proponents of pseudoaddiction …. In contrast, six articles, none with pharmaceutical support, questioned pseudoaddiction as a clinical construct."[282] Further, the authors wrote, "In conclusion, we find no empirical evidence yet exists to justify a clinical 'diagnosis' of pseudoaddiction."[283] I agree that there is no empirical evidence to justify a diagnosis of pseudoaddiction, and that use of this term was spread by the manufacturers of prescription opioids, with the explicit and dangerous message to doctors that more opioids should be prescribed.

e. To "correctly define addiction" the PPSG took consensus definitions from the American Society of Addiction Medicine, American Academy of Pain Medicine, and the American Pain Society.[284] Those included a definition

[281] *Id.* at p. 365.
[282] Greene MS, Chambers RA. Pseudoaddiction : Fact or Fiction ? An Investigation of the Medical Literature. 2015:310-317. doi:10.1007/s40429-015-0074-7, at p. 310.
[283] *Id.* at p. 314.
[284] WIS_PPSG_002042, June 8, 2001.

of the term "pseudoaddiction: "Pseudoaddiction is a term which has been used to describe patient behaviors that may occur when pain is undertreated. Patients with unrelieved pain may become focused on obtaining medications, may "clock watch," and may otherwise seem inappropriately "drug seeking." Even such behaviors as illicit drug use and deception can occur in the patient's efforts to obtain relief. Pseudoaddiction can be distinguished from true addiction in that the behaviors resolve when pain is effectively treated."[285] Thus, PPSG, an entity funded by the Pharmaceutical Opioid Industry, aligned with and promoted the Industry-supported view of "pseudoaddiction" as a real diagnosis for which more opioids were the prescribed treatment. (See Appendix II to this report).

8. The Pharmaceutical Opioid Industry encouraged and promoted several misconceptions concerning opioid use, including characterizing opioid dependence as a benign state that is easily reversible. Prescription opioids induce physiological dependence almost universally, and dependence leads to addiction in a significant subset of users, particularly as dose and duration of exposure are increased. Once established, opioid dependence represents a complex, debilitating, and sometime irreversible clinical problem. In most cases, these patients require a protracted medically supervised taper to lower their doses. In some cases, the suffering from withdrawal is so extreme that patients say they would rather die than go through it. Indeed people can die from opioid withdrawal, due to vital sign instability, suicide, and other complications.

a. Opioids cause neuroadaptation[286] and lead to tolerance, physiologic dependence, and painful withdrawal, even without the more complex biopsychosocial disease of addiction. As such, tolerance, dependence, and withdrawal in and of themselves represent real harm to patients as a result of opioid therapy. Due to tolerance, dependence, and withdrawal, many patients taking prescription opioids today will require an enormous investment of resources to help them get off of opioids or onto lower, safer doses. (See section on "Ending the epidemic" for a fuller description of what is required to help this population.)

b. Physiologic dependence, as currently defined by the DSM-5, is not the same as addiction. Dependence is the process whereby the body comes to rely on the drug to maintain biochemical equilibrium. When the drug is not available at expected doses or time intervals, the body becomes biochemically dysregulated, which manifests as the signs and symptoms of withdrawal. Although opioid dependence as currently defined is not the same as addiction, dependence on opioids can be associated with significant morbidity and mortality, and thus is not the same thing as dependence on other medications used as evidence-based treatment for

[285] *Id.*
[286] Koob, *et al.*, "Neurocircuitry," fn. 14, above, at p. 557.

illness.[287] Also, while dependence is defined differently from addiction, the line between them is not well-defined; in particular, the evidence of addiction often comes when an opioid-dependent patient attempts to taper and discovers that the loss of the drug causes the craving and compulsion that define addiction. In my clinical experience, dependence in some individuals can develop quickly. This clinical experience is consistent with studies showing that even short-term prescriptions of opioids for acute injuries result in long-term use of opioids after the acute condition has passed.[288] In the DSM-4, the edition prior to the DSM-5, "opioid use disorder" was called "opioid dependence." The new DSM-5 criteria made it more difficult to diagnose Opioid Use Disorder (opioid addiction), by removing the criteria of withdrawal, and tolerance from the definition in the case of a patient taking prescribed opioids under a doctor's care. The DSM-5 thereby reduced the proportion of patients who could be diagnosed with opioid use disorder.

c. On May 18, 2006, Purdue's David Haddox received the "excellent news" from Sidney Scholl, of Pinney Associates, that "Chuck O'Brien will be heading up the SUD [Substance Use Disorder] section of the DSM-V. This means that there is a good chance that 'addiction' will replace 'dependence' and there can be some changes in the diagnostic criteria that will reflect issues related to abuse and addiction of prescription opioids. Chuck asked me to assist him in this process. I would appreciate your input in this process. … If Marc Schuckit, who was originally slated to head up the SUD section, was still in charge, we would not be in this position as he likes the use of dependence over addiction. This is an opportunity we should not overlook, as major revisions of the DSM do not occur very often." Haddox wrote back, "This is really good news, Sid."[289]

d. On March 24, 2008, Haddox wrote to Phillipp Lippe in response to Lippe's request for comments regarding the American Medical Association's Report on Substance Abuse. Haddox wrote, "I am glad to see AMA getting into this area. Certainly the definitions and diagnostic criteria need some work…we are all fortunate that Charles O'Brien is the head of the substance use disorders section."[290]

e. On November 6, 2008, Haddox wrote to Chuck O'Brien, "It was good to see you this past weekend at ICPCD [International Conference on Pain and Chemical Dependency]. I really am excited that you are educating your nonclinical colleagues about the need for diagnostic nomenclature

[287] Lembke, *et al.*, "Weighing the Risks," fn. 3, above.
[288] Delgado M, Al. K et. National Variation in Opioid Prescribing and Risk of Prolonged Use for Opioid-Naive Patients Treated in the Emergency Department for Ankle Sprains. *Ann Emerg Med*. 2018, at p. 1; see also Howard, *et al.*, "Association of Prescribing," fn. 125, above, at p. E-6.
[289] PPLP004058443.
[290] PPLPC031000425439.

that are applicable in the real (read:clinical) world." Haddox went on to ask O'Brien to consult on a tamper-resistant opioid analgesic work group, and referenced prior payment of $2400 at O'Brien's rate of $600 per hour, "when it was anticipated that you would accompany us to the FDA Advisory Committee in March." Haddox added, "Also, in the interest of public health and medicine, I don't want to do anything to impair your ability to complete your DSM-V duties." O'Brien wrote back on November 12, 2008, to "Dave, I would be very happy to do this but it would simplify my life with Penn if we could considered this activity an extension [of] my efforts of several months ago where I already signed a contract." Haddox replied to that he was "really pleased that you will be able to work with us on this."[291]

f. On March 25, 2008, Haddox again exchanged emails with Phillipp Lippe. Dr. Lippe expressed concern that under DSM-IV, the first three criteria for diagnosis of substance dependence "are inherent in pain management," that is, "(1. Tolerance; (2) withdrawal symptoms; and (3) increased dosage or length of use." Haddox wrote to Lippe, "I have great confidence that the DSM-V will improve on this language, based on the chair of the SUD [committee]."[292]

g. This sequence of events indicates that Purdue's consultant, O'Brien, who was on a first name basis with Haddox, was responsible for the work that altered the DSM-V definition of opioid use disorder in a manner that suited Purdue's goals by distinguishing between "dependence" on the one hand, and "use disorder" or "addiction" on the other. This history is consistent with a larger effort on the part of Purdue to characterize dependence as a benign condition entirely separate from addiction. In reality, dependence, withdrawal, and tolerance, are closely linked to the disease of addiction, and from a neurobiological perspective, may be identical phenomena.

h. Ohio statutory definition of "Drug dependent person" means "any person who, by reason of the use of any drug of abuse, is physically, psychologically, or physically and psychologically dependent upon the use of such drug, to the detriment of the person's health or welfare."[293] Like the DSM-5, the Ohio definition makes a distinction between "physically" and "psychologically" dependent, and includes both of these phenomena as types of harm. In other words, according to Ohio law, the "drug dependent person" includes both persons with opioid use disorder/addiction (DSM-5 definition) and persons who are physically dependent on opioids, even if not addicted. I would agree with this definition.

[291] PPLPC018000252189, at pp. 190-191.
[292] PPLPC018000201219, at pp. 1219-1222.
[293] Ohio Revised Code §3719-011.

i. Regardless of these changing and disparate definitions, the bottom line has not changed: prescription opioids induce physiological dependence almost universally, and result in addiction in a significant subset of users, particularly as dose and duration of exposure are increased. Both represent significant harms.

j. Even limited exposure to opioids through a doctor's prescription, can lead to persistent opioid use. In other words, once patients start opioids, they are at high risk to continue them beyond the time of injury.

i. Brummett *et al.* sought to determine the incidence of new persistent opioid use after minor and major surgical procedures. Using a nationwide insurance claims data set from 2013 to 2014, they calculated the incidence of persistent opioid use for more than 90 days among opioid-naive patients after both minor and major surgical procedures. The authors found the rates of new persistent opioid use were similar between the two groups, ranging from 5.9% to 6.5%. By comparison, the incidence in the nonoperative control cohort was only 0.4%. The authors wrote, "New persistent opioid use represents a common but previously underappreciated surgical complication that warrants increased awareness."[294] The more opioids prescribed after surgery, the more patients tend to use. The number of opioid pain pills prescribed after surgery is a bigger predictor of how many opioids the patient will use, than is self-reported pain.

ii. A study by Delgado *et al.* looked at opioid naïve patients being treated for a common minor injury, ankle sprain, in the emergency department (ED) to determine the association between initial opioid prescription intensity and transition to prolonged opioid use. The authors concluded that opioid prescribing for ED patients treated for ankle sprains is "common," and prescriptions greater than 225 MED were associated with approximately five times higher rates of prolonged opioid use than with lower MED exposure. As the authors stated, "This is concerning because these prescriptions could still fall within 5- or 7-day supply limit policies aimed at promoting safer opioid prescribing."[295]

k. Clinical experience and clinical studies demonstrate that the majority of opioid legacy chronic pain patients (that is, patients who have been taking opioids daily for months to years) are physiologically dependent on opioids and struggle to taper, even when opioids pose imminent risk.

[294] Brummett CM, Waljee JF, Goesling J, *et al.* New persistent opioid use after minor and major surgical procedures in us adults. *JAMA Surg*. 2017., at p. 1.
[295] Delgado, *et al.*, "National Variation," fn. 288, above, at p. 1.

i. Withdrawal refers to the physiologic manifestations of not having the substance, the symptoms of which vary from substance to substance. As a general albeit oversimplified principle, the characteristics of withdrawal from a given substance are the opposite of intoxication for that substance. Withdrawal from opioids includes dysphoria (unhappiness), anxiety, insomnia, agitation, restlessness, muscle fasciculations, increased heart rate, elevated blood pressure, diarrhea, nausea, vomiting, and body pain. In some cases, the suffering is so extreme that patients say they would rather die than go through it. Although opioid withdrawal is generally thought to be painful but not life threatening, people can die from opioid withdrawal, due to vital sign instability, suicide, and other complications.[296]

ii. In a study at Oregon Health & Sciences University, after a hospital and clinic wide policy was implemented to get high dose legacy patients' doses down below 120 MED per day, including intensive physician education from 2011 to 2013,[297] 71 (63%) continued high-dose opioids in the post-intervention period.[298] In other words, even with a hospital wide initiative, a minority of patients tapered to safer doses.

iii. In a Danish study in which subjects were tapered off of opioids by reducing by 10% of the daily opioid dose every week until discontinuation,[299] only 13 of 35 patients randomized to the opioid taper completed the study without dropping out. The authors wrote "Although our study is hampered by a vast dropout rate, we still feel that it is highly justified to point to the fact that the stabilization of opioid treatment is not a simple task and opioid tapering off seems to be extremely difficult in CNCP patients in general…."[300]

l. Based on the literature and my own experience, I have worked with others to develop a protocol for safely and compassionately tapering opioid-dependent patients to lower doses or to eliminate them entirely. See discussion of the "BRAVO Protocol" below.

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[296] Stark MM, Payne-James J. People can die from opiate withdrawal. *Med Sci Law*. 2017;57(2):103. doi:10.1177/0025802417704600 at p. 103; see also Bohnert, *et al.*, "Association Between Prescribing Patterns," fn. 272, above, at p. 77.
[297] Weimer MB, Hartung DM, Ahmed S, Nicolaidis C. A chronic opioid therapy dose reduction policy in primary care. *Subst Abus*. 2016;37(1):141-147, at pp. 141-142.
[298] *Id.* at p. 114.
[299] Kurita GP, Højsted J, Sjøgren P. Tapering off long-term opioid therapy in chronic non-cancer pain patients: A randomized clinical trial. *Eur J Pain*. 2018;22(8):1528-1543, at p. 1531.
[300] *Id.* at p. 1536.

m. Defendants' promotional documents conveyed the message that prescription opioid dependence is not a significant concern, and that patients can be easily tapered off their prescriptions in a brief period of time. That message is contradicted by the scientific literature, my own experience, and patients' own accounts.[301] This messaging improperly contributed to physicians' false sense of security in the belief that prescription opioids can be prescribed without substantial risk. (See Appendix I). Further, misleading statements by Defendants on the efficacy of opioids in the treatment of chronic pain (see Appendix I), are challenged by the findings that pain improves in many chronic pain patients who are tapered down and/or off of opioids.

9. The Pharmaceutical Opioid Industry encouraged and promoted several misconceptions concerning opioid use, including inaccurate claims as to the validity of patient screening as a predictor of who will become addicted. The largest risk factors for addiction are dose and duration of opioid exposure, regardless of whether a particular patient may have identifiable risk factors in his or her social or genetic history. It is difficult, if not impossible, to predict in advance who will and will not get addicted to a prescription opioid. When it occurs in patients taking opioid medications for pain, addiction is neither easy to identify nor easily managed.

a. Over the course of the marketing of opioids for chronic pain, as the epidemic of addiction has grown, a number of physicians have attempted to develop "screening" instruments that might identify patients at high risk of addiction, who could then be screened out of opioid therapy, or closely monitored if such therapy were instituted. However, even if screening for established risk factors were implemented, data support the conclusion that OUDs would not be eliminated. In the Edlund study, the odds ratio for the incidence of OUDs associated with chronic use, even at low doses, was far higher than the odds ratio for established risk factors that screening instruments attempt to identify. In particular, the odd ratios with chronic low dose use (14.92), medium (28.69), and high dose (122.45) were all substantially greater than the odd ratios for mental health diagnosis (3.12); multiple mental health diagnoses (5.71); prior alcohol use disorder (3.22); and prior non-opioid abuse disorder (8.26).[302] For chronic/high dose opioid use, the odds ratio of approximately 122 is 40 times greater than for a mental health or alcohol use diagnosis, and 15 times higher than for a prior non-opioid use disorder. According to these data, the chronic use of opioids is responsible for far more OUDs than the existence of identifiable risk factors for OUDs.

b. It is true that *a priori* risk of addiction is related to genetics (a biological parent or grandparent with addiction), as well as complex psychosocial

[301] Rieder TN. In opioid withdrawal, with no help in sight. *Health Aff*. 2017;36(1):182-185. doi:10.1377/HLTHAFF.2016.0347

[302] Edlund, *et al.*, "Role of Opioid Prescription," fn. 25, above, at p. 563.

factors such as co-occurring mental illness, poverty, unemployment, multigenerational trauma, and peer influence. Persons with a history of addiction are more likely to develop problematic opioid use to the opioid their doctor is prescribing.[303] These risk factors notwithstanding, it is also true that addiction can occur in persons with none of these risk factors, and it is difficult, if not impossible, to predict in advance who will and will not get addicted to a prescription opioid. Hence, caution and monitoring are necessary for all patients being prescribed these medications, and even then will never be a failsafe method.

c. A validated screening instrument to predict which patients are more vulnerable to the adverse consequences of opioid therapy, including addiction, is theoretically of benefit, but to date, none has been shown to predict future adverse consequences. Kaye *et al.* summarizes the progress in a narrative review as follows: "Although several screening instruments and strategies have been introduced in recent years, there is no single test or instrument which can reliably and accurately predict those patients not suitable for opioid therapy or identify those who need increased vigilance or monitoring during therapy."[304]

d. Chou et al, in reviewing four studies that evaluated the accuracy of risk assessment instruments, found that three studies reported "inconsistent results" for the 10-item Opioid Risk Tool …. No study evaluated the effectiveness of risk mitigation strategies for improving outcomes related to overdose, addiction, abuse, or misuse."[305]

e. Indeed the Opioid Risk Tool, which was touted by Defendants for screening patients who could 'safely' be prescribing opioids, has recently been invalidated. "In this population, we were not able to replicate the findings of the initial ORT study. Self-report was no better than chance in predicting those who would have an opioid aberrant behavior. The ORT risk variables did not predict aberrant behaviors in either gender group. There was significant disparity in the scores between self-reported ORT and the ORT supplemented with medical record data (enhanced ORT)."[306]

f. There is a potential risk of any opioid risk tool: that prescribers gain a false sense of knowing who can and cannot get addicted, when in fact the biggest predictors of opioid dependency and addiction are access to opioids in the first place, and dose and duration, not personal characteristics. Indeed this focus on risky patients, rather than the inherent

[303] Weisner CM, Campbell CI, Ray GT, *et al.* Trends in prescribed opioid therapy for non-cancer pain for individuals with prior substance use disorders. *Pain.* 2009;145(3):287-293, p. 292.
[304] Kaye A, Jones M, Kaye A, *et al.* No Prescription Opioid Abuse in Chronic Pain: An Updated Review of Opioid Abuse Predictors and Strategies to Curb Opioid Abuse: Part 1.Title. *Pain Physician J.* 2017, at p. 573.
[305] Chou, *et al.*, Effectiveness and Risks – Systemic," fn. 60, above, at p. 280.
[306] Clark, *et al.*, "Re-assessing the Validity of ORT," fn. 144, above, at p. 1382.

risk associated with opioids themselves, has been the prevailing thinking in the 1980's, 1990's, and 2000's, encouraged by the Defendants' promotional messages, and is in part responsible for the opioid epidemic we face today. Prescribers were incorrectly taught that by screening out high risk patients, they would avoid opioid misuse and addiction.

g. Further, because of Defendants' aggressive promotion of the great benefits and minimal risks of prescribing opioids for pain, it would have been reasonable for doctors to conclude that there was little or no need for screening.

h. Finally, it is unlikely that asking patients about risk factors will ever be a suitable method of screening, as motivation to minimize or omit risk factors in pursuit of obtaining a specific type of drug will weigh heavily on the truthfulness and transparency of reporting (See discussion of Fleming study, above).

10. In sum, the Pharmaceutical Opioid Industry made misleading marketing claims to promote the above misconceptions, in the absence of reliable scientific evidence. Taken together, these misconceptions were the single most significant factor giving rise to the massive increase in the sale of opioids and the resulting epidemic of dependence and addiction, as detailed in this Report. Further, the actions of the Pharmaceutical Opioid Industry significantly influenced doctors and others who made decisions that increased the population's exposure to prescription opioids. Other developed countries with similar populations that experience chronic pain, but which have not had the same aggressive marketing as in the U.S., have not experienced any comparable degrees of prescription opioid overuse, mortality, and morbidity, supporting the conclusion that the marketing is the factor that made the difference.

a. To understand how insidious, pervasive, and misleading the opioid marketing was (and continues to be to this day), it is relevant to examine a published peer reviewed article in the medical literature on pain and opioids, dissect the misleading science contained therein, trace the affiliation of its authors back to opioid manufacturers, and uncover how a 'scientific article' was then used by opioid manufacturers as promotional material. In other words, peer reviewed articles written by key opinion leaders and/or sponsored by the Defendants, were disseminated to prescribers under the guise of science, when in fact they represented marketing tools. To illustrate, an example is provided below.

i. A report by Endo Pharmaceuticals created for its sales representatives included reference to an article by Katz et al, "A 12-week, randomized, placebo-controlled trial assessing the safety and efficacy of oxymorphone extended release for opioid naive

patients with chronic low back pain."[307] This article was cited as support for "Key Feature Messages" in the Endo document providing "suggested approach for call planning."[308]

A. The Katz study included Endo employees as authors and was Endo sponsored.[309]

B. In the "Key Features Messages" used to train Endo's sales staff, one of the claim messages they were instructed to convey, ostensibly based on the Katz article, was that over 70% of patients on oxymorphone extended release (Opana ER) achieved greater than 50% pain relief. ."[310] In reality, this is a misleading figure for the reasons below.

C. The ">70%" figure, who purportedly achieved > 50% pain reduction, was based on only the fraction of patients randomized to Opana who were able to complete the randomized controlled trial. In reality, 325 patients were recruited for the open label "enriched enrollment" phase which exposed all 325 to Opana, and 120 discontinued before the randomized controlled trial (RCT) even began. So only 63% (205/325) could tolerate Opana at all, let alone achieve >50% pain relief. Furthermore, following the initial enriched enrollment phase, another 33% of the subjects randomized to Opana also failed to complete the trial due to adverse effects or lack of efficacy.[311]

D. By ignoring the substantial percentage of patients who could not tolerate Opana at all (37%), and those who subsequently dropped out of the drug arm of the trial (33%), Endo trained its sales team to mislead physicians about its efficacy by making the false claim that "over 70%" achieved over 50% pain relief.

E. Further, although the Katz article did not explicitly state that Opana can be used long-term for chronic pain, the training does not instruct the salesforce to limit use to 12 weeks.[312] Also note that the Hale study,[313] to be used for

[307] Katz M, Rauck R, Ahdieh H, *et al.* A 12-week, randomized, placebo-controlled trial assessing the safety and efficacy of oxymorphone extended release for opioid-naive patients with chronic low back pain. *Curr Med Res Opin*. 2007;23(1):117–128.
[308] ENDO-CHI_LIT-00210473 at 0475
[309] Katz, *et al.*, "12 Week Randomized Trial," fn. 307, above, at p. 117.
[310] ENDO-CHI_LIT-00210473 at 0475
[311] Katz, *et al.*, "12 Week Randomized Trial," fn. 307, above, at p. 120.
[312] ENDO-CHI_LIT-00210473 at 0474

the same sales calls, explicitly stated in the abstract that Opana provides "long-term analgesia," despite a study length of only 12 weeks.[314] The claim of "long-term analgesia" is misleading in the context of a 12-week study.

b. The impact of marketing material disseminated to prescribers under the guise of science cannot be overstated, especially in an era when practicing 'evidence based medicine' was and is the gold standard. The average busy clinician will never have time to wade through the voluminous literature, especially at the level of detail required to detect inaccuracies, and therefore relies on bottom line conclusions found in the abstract, trusting that a published peer reviewed article is a valid and reliable source.

c. In their report "Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use," The National Academies of Science, Engineering and Medicine stated, "… certain hypotheses about causes of the epidemic are inescapable … *heavy promotion of opioid prescribing by drug manufacturers (including misleading claims by some)* and substantially increased prescribing by physicians were key contributors to the increase in misuse, OUD, and accompanying harms."[315] (Emphasis added)

d. According to the U.S. Drug Enforcement Administration, in a letter in the appendix of the 2003 GAO report cited previously, Purdue's "aggressive methods, calculated fueling of demand …. Contributing to the abuse and diversion problem (and the product's excessive availability) …. in promoting this drug to practitioners, Purdue deliberately minimized the abuse risk associated with OxyContin…. The claim in Purdue's 'educational' video for physicians that opioid analgesics cause addiction in less than one percent of patients is not only unsubstantiated but also dangerous because it misleads prescribers."[316] The DEA letter stated further, that Purdue's distribution of branded promotional items such as fishing hats, stuffed animal plush toys and coffee mugs was "unprecedented for a Schedule II opioid", and served as "an indicator of Purdue's aggressive, excessive and inappropriate marketing of their product, OxyContin."[317]

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[313] Hale ME, Ahdieh H, Ma T, Rauck R. Efficacy and Safety of OPANA ER (Oxymorphone Extended Release) for Relief of Moderate to Severe Chronic Low Back Pain in Opioid-Experienced Patients: A 12-Week, Randomized, Double-blind, Placebo-controlled Study. *J Pain*. 2007;8(2):175-184.
[314] *Id.* at p. 175.
[315] National Academies of Science Engineering and Medicine, "Pain Management and Opioid Epidemic 2017," fn. 131, above, at pp. 40-41.
[316] Letter from Rogelio Guevara, Chief Inspector, DEA, to Marcia Crosse/GAO, 11/5/03; reprinted at GAO Report, "OxyContin Abuse," fn. 56, above, at pp. 56-57.
[317] *Id.* at p. 56.

e. As I wrote in my book, Drug Dealer, M.D.,[318] doctors were "duped" by the Pharmaceutical Opioid Industry into believing the myths of substantial benefits and very low risks of prescription opioids. I also wrote in my book that others had some responsibility for the events that have transpired. The roles of other parties are summarized below. In addition, on the basis of my review of documents that were provided to me in this case, I am more aware of the Pharmaceutical Opioid Industry's role in influencing some of those other parties to act in the way they did.

i. The Federation of State Medical Boards (FSMB) is a national organization that oversees the 70 medical and osteopathic boards of the United States and its territories. The State Board organizations serve many functions, but the most important is to police doctors, and exert disciplinary action against doctors who are deemed dangerous to patients. One of the most severe forms of disciplinary action is to revoke a doctor's license to practice medicine.

A. In 1998, the Federation of State Medical Boards released a policy to reassure doctors that they would not be prosecuted if they prescribed even large amounts of opioids, as long as it was for the treatment of pain. Further, the Federation urged state medical boards to punish doctors for under-treating pain. Doctors lived in fear of disciplinary action from the State Medical Boards, and the lawsuit that usually followed, if they denied a patient opioid painkillers. As detailed in Appendix II to this Report, the Pharmaceutical Opioid Industry provided substantial funding to the Wisconsin PPSG, which lobbied State Medical Boards to adopt its Model Policy to increase access to opioids, preclude punishment if opioids were prescribed for pain, and classify undertreatment of pain as inappropriate conduct.

B. In 2001, every licensed physician in the state of California was mandated to attend a day-long course on the treatment of pain, as a requirement to maintain licensure. I attended one of these courses, and to my recollection, all of the false messages promoted by the Defendants were highlighted in this CME course, including overstatement of benefits, and understatement of risks.

C. The Federation of State Medical Boards published a book promoting the use of opioid painkillers. This book was sponsored by a "consortium" that included Abbott

[318] Lembke, "*Drug Dealer, MD,*" fn. 2, above.

Laboratories, Alpharma Pharmaceuticals, Cephalon, Inc., Endo Pharmaceuticals, the Wisconsin PPSG, and Purdue Pharma[319]. (See Appendix II).

D. As detailed in Appendix II to this Report, the Pharmaceutical Opioid Industry provided substantial funding to the Wisconsin PPSG, which lobbied State Medical Boards to increase access to opioids, preclude punishment if opioids were prescribed for pain, and classify undertreatment of pain as inappropriate conduct. PPSG played a central role in revising the Federation of State Medical Board's Model Guidelines on the Use of Controlled Substances for Pain Management[320], now entitled Model Policy for the Use of Controlled Substances for Pain Management.[321]

ii. The Food and Drug Administration (FDA) is an agency within the U.S. Department of Health and Human Services responsible for assuring the safety, effectiveness, and quality of medical drugs. They are responsible for approving drugs before they reach the market, and monitoring the safety and marketing of those drugs after they are publicly available. In my book, Drug Dealer, MD, I assigned some responsibility for the prescription drug epidemic to the FDA, and to the Defendants for efforts to influence the FDA. However, it is my understanding that other witnesses with expertise on FDA-related matters will offer testimony on such issues at trial, and, accordingly, I do not intend to testify on issues relating to the FDA.[322]

iii. The Toyota-ization of Medicine

A. The majority of doctors today work in large integrated health care systems. During the 1990's and 2000's, there occurred a mass migration of doctors out of private practice and into managed care organizations. In 2002, 70% of U.S. physician practices were physician-owned. By 2008, more than 50% of U.S. physician practices were owned and

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[319] Fishman, S.(ed.), "Responsible Opioid Prescribing: A Physician's Guide" (Federation of State Medical Boards, Waterford Life Sciences, 2007).
[320] WIS_PPSG_008292, 11/30/2005
[321] http://www.fsmb.org/Policy%20Documents%20and%20White%20Papers/2004_model_pain_policy.asp
[322] Lembke, "*Drug Dealer, MD,"* fn. 2, above; Fauber J. FDA and Pharma: Emails Raise Pay-for-Play Concerns. *Sentinal/MedPage Today*. October 7, 2003, see http://www.medpagetoday.com/PainManagement/PainManagement/42103,at p. 1.

operated by hospitals or integrated health delivery systems, and that number just continues to rise.[323]

B. The migration of doctors into integrated health care systems (hospital factories) has transformed medical treatment. Doctors work much less autonomously. Treatment options are often dictated by hospital administrators, (see Joint Commission) guidelines, and third-party payers (health insurance companies). The result is that doctors experience enormous pressure to get patients in and out quickly, to palliate pain, and to have 'satisfied customers.' This too has contributed to the problem of overprescribing.[324]

C. These structural factors opened the doors, but the aggressive marketing and misrepresentation of risks and benefits took advantage of these conditions to maximize sales and maximize harm.

D. I have also written, in "Drug Dealer, M.D.," about the manipulative behaviors of patients in attempting to obtain opioid drugs from their doctors. These behaviors are not surprising; in fact they are diagnostic of the disease of addiction, whether the drug is OxyContin, or Opana, or heroin. In my opinion, the Pharmaceutical Opioid Industry has attempted to blame victims of the disease of addiction for the epidemic resulting from their own aggressive promotion of addictive drugs, while at the same time promoting the false message that patients taking these drugs for pain under a doctor's prescription have little or no risk of addiction or overdose.

f. Opioid prescribing in the United States far exceeds that of other developed nations with aging populations and comparable population needs for pain relief.

i. Using International Narcotics Control Board figures, the United States consumed 173,332 kilograms of 574,693 kilograms of

[323] Kocher R, Sahni N. Hospitals ' Race to Employ Physicians — The Logic Behind a Money Losing Proposition. *NEJM*. 2011:1790-1793, at p. 1791.
[324] Lembke A. Why Doctors Prescribe Opioids to Known Opioid Abusers. *N Engl J Med*. 2012;367(17):1580-1581.

opioids consumed globally (382,131.6 of 1,266,981.2 pounds), or 30.2 percent.[325]

ii. Using "defined daily doses," the United States consumed the most opioids per unit population from 2013 to 2015: 47,580 doses of narcotic drugs were consumed per day per million people. Canada comes in second with 34,444 defined doses consumed per million people per day, and Germany in third with 30,796; Japan was 50th at 1,223 defined doses/day.[326]

g. Attached to this Report is an Appendix of statements made by the Defendants in this litigation, which were contrary to medical and scientific evidence, or not sufficiently supported by the evidence to justify the enormous risks entailed by chronic opioid therapy. In broad terms, Defendants' assertions overstated the benefits and understated the risks of chronic opioid therapy, as specified in but not limited to the representations listed in the Appendix.

11. The increase in opioid sales resulted in a prescription opioid epidemic in the United States. "Epidemic," defined as an outbreak of disease that spreads quickly and affects many individuals at the same time, is the appropriate term to describe the increase in opioid related morbidity and mortality beginning in the 1990's and continuing to the present day. There is an undeniable link between suicide and opioids. This epidemic is first and foremost a prescription opioid epidemic, with prescription opioids accounting for a higher number of cumulative deaths to date (1999-2017) than heroin and illicit fentanyl combined.

a. Based on CDC data, between 1999 and 2017, 230,869 people died from opioid pain relievers (excluding non-methadone synthetics, predominantly fentanyl). In the same time period, 100,599 died from heroin, and 93,151 people died from non-methadone synthetics (predominantly fentanyl), for a total of 193,750 deaths due to heroin and illicit fentanyl. Although these numbers are staggering, the cumulative death toll from opioid pain relievers (230,869) is more than that of heroin and illicit fentanyl combined (193,750).[327] In short, while there has been an obvious recent spike in deaths related to heroin and illicit fentanyl, the number of deaths caused by non-fentanyl prescription opioids remains unacceptably high, and cumulatively exceeds deaths associated with heroin and fentanyl.

Prescription opioid related deaths, excluding fentanyl and methadone, did not decline from 2016 to 2017, the last year for which CDC data are available, but in fact remained essentially identical (14,487 deaths in 2016;

[325] International Narcotics Control Board, Narcotic Drugs Technical Report 2016, at pp. 200-203. See https://www.incb.org/incb/en/narcotic-drugs/Technical_Reports/2016/narcotic-drugs-technical-report-2016.html.
[326] *Id.* at pp. 226-228.
[327] Centers for Disease Control and Prevention, *Data Brief 329. Drug Overdose Deaths in the United States, 1999–2017*. https://www.cdc.gov/nchs/data/databriefs/db329_tables-508.pdf#page=1, at p. 4.

14,495 deaths in 2017).[328] A report just released by the CDC shows that drug overdose deaths in women aged 30–64 years due to prescription opioids have been steadily rising between 1999 and 2017. "The crude rate for deaths involving prescription opioids increased from 1999 to 2017 for every age group, with the largest increases (>1,000%) among women aged 55–64 years."[329]

b. An article published in Science in 2018 by Jalal, et al, "Changing Dynamics of the Drug Overdose Epidemic in the United States from 1979-2016,"[330] suggests that mortality data from numerous "drug-specific subepidemics" can be fitted to a smooth exponential curve during that time period. However, the authors note the "paradox" presented by these results, since the data combine mortality associated with subepidemics as disparate as heroin and fentanyl deaths in the northeastern United States with methamphetamines in the southwestern states.[331] Accordingly, an after-the-fact fitting of 38 years of combined data to a smooth curve does not obviate the need to understand each subepidemic on its own terms. In the case of prescription opioids, factors relevant to that epidemic have been addressed throughout this report, and are summarized as follows:

   i. The sheer scale of access to opioids made possible through opioid overprescribing during this time period, led individuals who otherwise would never have been exposed, to use and subsequently be killed by opioids.

   ii. The lethality of opioids sets opioids apart from other drugs. Indeed the apparent continuity of the overdose mortality rate curve in the Jalal *et al.* article, on closer inspection, shows a definitive rise above the smooth curve between 2001 and 2010, corresponding to the prescription opioid epidemic.[332]

   iii. An efficient distributor supply chain made prescriptions opioids available on a mass scale to large numbers of people in rural and remote settings, expanding both the licit and illicit drug market, and sets this opioid epidemic apart from prior epidemics and other drug epidemics.

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[328] *Id.* at p. 4.
[329] VanHouten JP, Rudd RA, Ballesteros MF, Mack KA. Drug Overdose Deaths Among Women Aged 30–64 Years — United States, 1999–2017. *MMWR Morb Mortal Wkly Rep*. 2019;68(1):1-5, at p. 2.
[330] Jalal H, Buchanich JM, Roberts MS, Balmert LC, Zhang K, Burke DS. Changing dynamics of the drug overdose epidemic in the United States from 1979 through 2016. *Science (80-)*. 2018. doi:10.1126/science.aau1184.
[331] *Id.* at p. 1.
[332] *Id.*

iv. The problem of addiction more broadly in society and culture today does not negate the significant role of opioids manufacturers and distributors in causing this epidemic.

v. Although forces may be operative to accelerate demand, such as despair, loss of purpose, and dissolution of communities, studies show that the 'push' of increased access to opioids has played a bigger role than the 'pull' of despair.[333]

c. Opioid deaths are only one measure of this epidemic

i. 11 million people misused prescription opioids in 2016, compared to the approximately 1 million people using heroin. In 2011, according to a CDC report, 11 million people reported nonmedical use of opioid analgesics. "Moreover, chronic nonmedical use of opioid analgesics (i.e. nonmedical use on 200 days or more in the past year) increased roughly 75% between 2002-2003 and 2009-2010 .This increase means that on average in 2009-2010 there were nearly 1 million people in the U.S. with chronic nonmedical use of opioid analgesics."[334]

ii. Nearly 2 million (0.8%) of people in the United States are addicted to opioids based on estimates from the 2015 National Survey on Drug use and Health (NSDUH).[335]

iii. According to the CDC, among approximately 45 million emergency department visits reported by the 16 Enhanced State Opioid Overdose Surveillance (ESOOS) states from July 2016 through September 2017, "a total of 119,198 (26.7 per 10,000 visits) were suspected opioid overdoses. Opioid overdose ED visits increased 34.5% from third quarter 2016 to third quarter 2017 …. Ten states experienced significant increases in prevalence during this period, although substantial variation was observed among states in the same region. …. All states in the Midwest reported significant increases, including Wisconsin (108.6%), Illinois

[333] Ruhm CJ. Deaths of Despair or Drug Problems? NBER Working Paper No. 24188, NBER Program(s):Health Care, Health Economics, Public Economics (2017).

[334] United States Department of Health and Human Services. Addressing Prescription Drug Abuse in the United States. :1-36, at pp., 9-10. See https://www.cdc.gov/drugoverdose/pdf/hhs_prescription_drug_abuse_report_09.2013.pdf

[335] Han B, Compton WM, Blanco C, Crane E, Lee J, Jones CM. Prescription Opioid Use, Misuse, and Use Disorders in U.S. Adults: 2015 National Survey on Drug Use and Health. Annals of internal medicine. 2017;167(5):293-301. Epub 2017/08/02. doi: 10.7326/m17-0865. PubMed PMID: 28761945, at p. 293.

(65.5%), Indiana (35.1%), Ohio (27.7%), and Missouri (21.4%)."[336]

iv. Unlike the available fatal overdose data, which are categorized according to non-fentanyl prescription opioids, heroin, etc., the CDC/ESOOS on emergency department visits are not broken out into categories. Although the cumulative total of prescription opioid mortality since 1999 exceeds mortality for fentanyl plus heroin, the mortality rate for the latter category has recently begun to exceed the former; it is likely that the nonfatal overdose hospital admissions have occurred in a similar ratio of prescription opioids to illicit heroin and fentanyl.

v. As described previously, tens of thousands of Americans experience non-fatal overdose, both in medical settings, like the emergency department, and in the field, creating a significant burden on the health care system and on first responders, not to mention the victims of near overdose themselves. In a paper by Dunn et al,[337] previously discussed, the over 14,000 fatal prescription opioid overdoses in 2017[338] would translate to over 100,000 nonfatal overdoses during that same year. While fatal cases justifiably capture our attention, it must also be recognized that the cost of a nonfatal overdose is far greater in terms of medical and community resources, to treat the overdose episode itself, and to provide long-term care for the OUD disease that gave rise to the event.

12. We are now in the second and third waves of this epidemic, with a spike in deaths from illicit opioids, particularly heroin (second wave) and illicit fentanyl (third wave). There is a clear link between prescription opioid exposure and the subsequent use of heroin and other illicit opioids. The likelihood of heroin addiction is 40 times greater in those who have previously misused or been addicted to prescription opioids, and fentanyl, in turn, has contaminated the heroin supply.

a. "A preponderance of evidence suggests that the major increase in prescription opioid use beginning in the late 1990s has served as a gateway to increased heroin use[339]… The interrelated nature of the

[336] Vivolo-Kantor AM, Seth P, Gladden RM, Mattson CL, Baldwin GT. Vital Signs : Trends in Emergency Department Visits for Suspected Opioid Overdoses — United States , July 2016 – September 2017. 2018;67(9):279-285, at p. 281.
[337] Dunn, *et al.*, "Opioid Prescriptions," fn. 268, above.
[338] CDC, Data Brief 329, fn 327, above, at p. 4.
[339] National Academies of Science Engineering and Medicine (NASEM), "Pain Management and Opioid Epidemic 2017," fn. 133, above, at p. 215.

prescription and illicit opioid epidemics means that one cannot be addressed separately from the other."[340]

b. In the 1960s, 80% of opioid users reported that their first exposure to opioids was in the form of heroin. In the 2000s, 75% of opioid users reported that their first exposure to opioids was in the form of prescription painkillers.[341]

c. The incidence of heroin use among people who reported prior nonmedical use of prescription opioids was 19 times as high as the incidence among persons who reported no previous nonmedical use.[342]

d. Prescription opioid use disorder/addiction is associated with a likelihood of heroin addiction that is 40 times as great as the likelihood with no prescription-opioid misuse or addiction, even after accounting for sociodemographic, geographic, and other substance abuse or dependence characteristics.[343]

e. Eighty-six percent of urban people who used injected heroin in New York and Los Angeles in 2008 and 2009 had used opioids nonmedically before using heroin.[344] Similar studies conducted in San Diego, Seattle, and New York showed that 40%, 39%, and 70% of heroin users, respectively, reported that they had used prescription opioids nonmedically before initiating heroin use.[345]

f. Muhuri found that 79.5% of persons who recently began using heroin had used prescription opioids nonmedically before initiating heroin use.[346]

g. The number of Americans aged 12 and older with past month heroin use, rose from 281,000 to 335,000 between 2011 and 2013, a significant increase from the 166,000 using heroin in 2002.[347]

h. Deaths due to illicit fentanyl have also been on the rise. Fentanyl is 50-100 times as potent as heroin, and when mixed in with heroin or other illicit

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[340] *Id.* at p. 248.
[341] Cicero TJ, Ellis MS, Surratt HL, Kurtz SP. The changing face of heroin use in the united states: A retrospective analysis of the past 50 years. *JAMA Psychiatry*. 2014. doi:10.1001/jamapsychiatry.2014.366, at p. E-1.
[342] Muhuri PK, Gfroerer JC, Davies MC. Associations of nonmedical pain reliever use and initiation of heroin use in the united States. *CBHSQ Data Rev*. 2013;(August):1-16, at p. 1.
[343] Compton WM, Jones CM, Baldwin GT. Relationship between Nonmedical Prescription-Opioid Use and Heroin Use. *N Engl J Med*. 2016. doi:10.1056/NEJMra1508490, at p. 157.
[344] Lankenau SE, Teti M, Silva K, Bloom JJ, Harocopos A, Treese M. Initiation into prescription opioid misuse amongst young injection drug users. *Int J Drug Policy*. 2012;23(1):37-44, at p. 41.
[345] Compton, *et al.*, "Relationship Between Opioid and Heroin Use," fn. 343, above, at p. 156.
[346] Muhuri, *et al.*, "Associations of NMPR and Heroin," fn. 342, above, at p. 1.
[347] McCarthy M. Illicit drug use in the US holds steady, but heroin use is on rise. *BMJ*. 2013;347(September):f5544. doi:10.1136/bmj.f5544, at p. 1.

drugs without the users' knowledge, an unsuspecting user is more vulnerable to overdose.

i. In my opinion, the epidemic of prescription opioid use beginning in the 1990s has been a significant factor contributing to the subsequent increase in heroin and fentanyl use. As the data show, the use of addictive prescription opioids commonly precedes the use of addictive heroin and fentanyl.

13. The increased sales of prescription opioids harmed communities by causing individuals who otherwise would not have been exposed to opioids, to be exposed and become addicted, including individuals who turned from prescription opioids to illicit sources of opioids such as heroin (The Gateway Effect).

a. The Purdue "Project Tango" Power Point presentation, referenced above, includes the following quote on the slide that shows the definition of addiction along with the statistical data on the numbers and growth rate of addiction: "'This can happen to any-one—from a 50 year old woman with chronic lower back pain to a 18 year old boy with a sports injury, from the very wealthy to the very poor.' Pain specialist Cornell Weill, 100 patients/week."[348] I agree with this statement, and it is relevant to "The Gateway Effect," whereby the trajectory to addiction begins with exposure to prescription opioids. (Note: a statement like this never made an appearance in Purdue material, internal or external, when they were marketing opioids for pain, but is now front and center as they pursue the addiction treatment market. Indeed when it came to marketing opioids for pain, Purdue and other Defendants pushed the idea that only a few vulnerable "addicts" could get addicted, and that the vast majority of patients were somehow immune.)

b. Teens are especially vulnerable to the increased access to prescription drugs. Adolescence is a time when the rapidly growing brain is more plastic, and therefore more vulnerable on a neurological level, to potentially irreversible brain changes caused by chronic drug exposure.[349] Teens are also more likely to take risks, without appreciating the adverse consequences associated with those risks.

c. As mentioned above, opioids are generally considered appropriate for cancer pain. However, patients with cancer related pain, even at the end of life, are not immune to addiction and they should be monitored carefully for addiction and other adverse consequences, and should receive the lowest dose for the shortest possible duration.

[348] PPLPC016000255303, produced natively at *9.
[349] HHS, "Addressing Prescription Drug Abuse," fn. 334, above, at p. 189.

i. A first person perspective piece in the New England Journal of Medicine, describes the experience of an oncologist (cancer doctor) whose patient gets addicted to opioids.[350] In my clinical experience, opioid misuse and addiction are as common among cancer patients as non-cancer patients.

ii. There were more than 15 million cancer survivors in the United States in 2016.[351] Even patients with cancers once considered incurable, now go into remission for decades and more, emphasizing the need for caution in treating a very large population of patients with opioids.

14. The increased sales of prescription opioids harmed communities by causing individuals who otherwise would not have been exposed to opioids, to become dependent on opioids (independent of addiction), and suffer significant morbidity and mortality as a result (The Dependence Effect).

a. Over the last 30 years, the liberal prescribing of opioids for chronic pain has created a "legacy" population of patients who have been on opioids for several years if not decades, and are now physically dependent on opioids, making it difficult to come off. There are no exact numbers on how many Americans are opioid dependent. In a Washington Post Kaiser Family Foundation survey of patients receiving opioids for pain, 34% report becoming physiologically dependent on prescription opioids.[352]

b. By 2005, long-term opioid therapy was being prescribed to approximately 10 million Americans. "In 2014 alone, U.S. retail pharmacies dispensed 245 million prescriptions for opioid pain relievers. Of these prescriptions, 65% were for short-term therapy (<3 weeks), but 3 to 4% of the adult population (9.6 million to 11.5 million persons) were prescribed longer-term opioid therapy."[353]

c. According to a 2019 study, prescribing of opioids has declined from its peak but still vastly exceeds the level of prescribing before the epidemic began in the 1990s, and prescription length continues to increase. Opioid prescriptions per person in the total US increased annually at an average rate of 6.9% per year until 2010, and decreased at an average rate of 3.8% per year from 2010 through 2015. In Ohio, MME per person increased by an average of 6.1% per year from 2006 through 2010; decreased on

[350] Loren AW. Harder to Treat Than Leukemia - Opioid Use Disorder in Survivors of Cancer. *NEJM*. 2018;379(26).
[351] Bluethmann SM, Mariotto AB, Rowland JH. Anticipating the "silver tsunami": Prevalence trajectories and comorbidity burden among older cancer survivors in the United States. *Cancer Epidemiol Biomarkers Prev*. 2016. doi:10.1158/1055-9965.EPI-16-0133, at p. 1029.
[352] Users P-K survey of long-term prescription opioid painkiller. Washington Post Kaiser Long-Term Prescription Opioid Painkiller Users Poll, Oct. 3-Nov. 9, 2016, at p. 10.
[353] Volkow, *et al.*, "Misconceptions and Mitigation," fn. 16, above, at p. 1253.

average by 6.7% per year from 2010 through 2015, and decreased 12.7% per year from 2015 through 2017.However, prescription duration increased in Ohio from 12.4 days in 2006 to 19.3 days in 2017.[354] Duration of exposure is a major risk factor for OUD.

d. A newborn is born dependent on opioids as a result of being exposed to opioids in utero. According to DSM-5 criteria, the opioid dependent newborn is not 'addicted,' because addiction requires the manifestations of certain pathological and maladaptive behaviors in conjunction with opioid use. The newborn is the passive recipient of opioids due to the mother's exposure.

i. The rate of admission to NICU [neonatal intensive care units] for neonatal abstinence syndrome (NAS), a drug-withdrawal syndrome that occurs after in utero exposure to opioids, increased from 7 cases per 1000 admissions to 27 cases per 1000 admissions between 2004 and 2013.[355]

ii. Tolia reported that "the median length of stay increased from 13 days to 19 days (P<0.001 for both trends). The total percentage of NICU [neonatal intensive care unit] days nationwide that were attributed to the neonatal abstinence syndrome increased from 0.6% to 4.0% (P<0.001 for trend), with eight centers reporting that more than 20% of all NICU days were attributed to the care of these infants in 2013."[356]

iii. This approximate quadrupling of the rate of NAS is directly attributable to the epidemic of opioid use disorder that began with promotion of prescription opioids and continues to the present, accompanied by use of illicit opioid drugs.

15. The increased sales of prescription opioids harmed communities by causing a dramatic increase in the widespread availability of opioids, including to persons for whom opioids had not been prescribed (The Tsunami Effect). Medical prescriptions are the primary conduit for prescription opioid misuse. Less than 10% of Americans misusing prescription opioids got them from a "street dealer."

a. It's important to recognize that although many of the communities hit hardest by the opioid epidemic were already struggling with serious social and economic problems, the sudden availability of and easy access to

[354] Schieber, L, Guy, G, *et al.*, Trends and Patterns of Geographic Variation in Opioid Prescribing Practices by State, United States, 2006-2017, at pp. 4-5.
[355] Tolia VN, Patrick SW, Bennett MM, *et al.* Increasing incidence of the neonatal abstinence syndrome in U.S. neonatal ICUs. *Obstet Gynecol Surv*. 2015. doi:10.1097/OGX.0000000000000243, at p. 2118.
[356] *Id.* at p. 2118.

opioids, initially in prescription pill form, contributed to the economic and social devastation of many towns across America.[357]

b. Economic downturn and the efflux of manufacturing jobs in towns across America in the last thirty years, have contributed to so-called "deaths of despair" – early mortality in middle aged non-Hispanic whites due primarily to drug overdose.[358] Nonetheless, economic disadvantage contributes only 10-20% of mortality risk attributable to opioids, whereas the larger share of risk is due to supply of opioids in a given geographic region.[359]

c. The opioid epidemic is partly responsible for the spread of Hepatitis C, HIV and other infectious diseases across the country in recent years, as people who become addicted to prescription opioids, transition to injection drug use and share needles with others who are infected. For example, the outbreak of Hep C and HIV in Scott County, Indiana in 2015, "resulted from inappropriate prescribing of opioid medications."[360]

16. Ending the epidemic of opioid addiction, dependence, and death will require significant investment of resources. An effective strategy will be multifaceted, and will accomplish the following: prevent new cases of addiction, dependence, and other related harms (primary prevention), limit progression of harm (secondary prevention), and treat existing cases (treatment). These changes will require curbing opioid prescribing, re-educating patients and health care providers, creating de-prescribing clinics, promoting naloxone and other harm-reduction strategies, and building an enduring medical infrastructure to treat addiction.

a. Primary prevention: Preventing new cases of the disease by limiting access to opioids, re-educating prescribers, and rebuilding communities devastated by the epidemic.

i. Opioids should not be prescribed as first line treatment for most forms of pain. Exceptions include cases of severe tissue injury, peri-operatively when multimodal analgesia is insufficient, and as palliative/end of life care.

A. For acute pain, the CDC guidelines recommend no more than 3 to 7 days of opioid treatment. Even within this general guideline, it is important to limit both the dose and frequency of administration of opioid drugs during the 3-7 day window, to minimize the increase in long-term use that

[357] Ruhm, *et al.*, "Deaths of Despair," fn. 333, above.
[358] Case A, Deaton A. Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century. *Proc Natl Acad Sci*. 2015. doi:10.1073/pnas.1518393112, at p. 15081.
[359] Ruhm, *et al.*, "Deaths of Despair," fn. 333, above.
[360] Strathdee SA, Beyrer C. Threading the Needle — How to Stop the HIV Outbreak in Rural Indiana. *N Engl J Med*. 2015. doi:10.1056/NEJMp1507252, at p. 398.

has been documented following higher doses of opioids for acute pain.[361]

B. First line treatment for pain should include non-opioid medications and non-medication treatment for pain (non-opioid medications, physical therapy, psychotherapy). The latter are especially important for the treatment of chronic pain.

C. There may be unusual instances when opioid medications can be used to good effect in the treatment of chronic pain; but even in this setting, avoiding daily use to avoid tolerance and dependence is recommended. Further, very close monitoring for the emergence of adverse medical consequences, including misuse and addiction, using objective criteria such as urine toxicology and database scrutiny, are essential components of a safe and effective treatment plan. Further, an exit strategy for cessation of opioid therapy is necessary, should risks outweigh benefits at any point in the treatment, in recognition that most patients will have become dependent and will taper with difficulty.[362]

ii. Data on the impact of interventions to curb opioid prescribing have recently become available supporting the view that limiting opioid prescribing in a systematic way reduces prescription opioid-related overdose deaths without adversely compromising pain treatment.

A. Massachusetts had the first of its kind state-wide acute care prescribing limits and a required-check of the Prescription Drug Monitoring Programs (PDMPs) prior to opioid prescribing. As a result they reduced opioid prescriptions by 30%.[363]

B. The Department of Public Health determines mean and median quantity and volume of prescriptions for opioids, within categories of similar specialty or practice types. Prescribers who exceed mean or median will be sent notice.[364]

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[361] Delgado, *et al.*, "National Variation," fn. 288, above, at p. 389.
[362] Dunn, *et al.*, "Opioid Prescriptions," fn. 268268, above, at p. 86.
[363] Massachusetts Department of Public Health Press Release, "Year Over Year Opioid-Related Overdose Deaths Decline in Massachusetts; Opioid Prescriptions Fall 30 Percent", August 24, 2018. See https://www.mass.gov/news/year-over-year-opioid-related-overdose-deaths-decline-in-massachusetts-opioid-prescriptions.
[364] *Id.*

C. The law establishes a drug stewardship program to be paid for by drug companies that makes it easier for patients to safety dispose of unwanted and unused medications. Effective Jan. 1, 2017.[365]

D. The State has launched core competencies for safe prescribing of opioids in the state's medical schools, community health centers, nursing, physician assistant, dental schools and schools of social work." (emphasis in original) Commensurate with decreases in opioid prescribing, Massachusetts has seen a decrease in opioid-related overdose deaths: "Opioid-related overdose deaths in Massachusetts have fallen steadily over the past three quarters even as the presence of fentanyl in overdose deaths reached an all-time high…Overall in 2017 there was a 4 percent decrease in opioid-related overdose deaths from 2016. The data also shows that the Commonwealth has experienced a 30 percent decline in opioid prescriptions since the launch of the Massachusetts Prescription Monitoring Program (MassPAT) in August 2016. [366]

E. A successful program in Chittenden County, Vermont achieved a 50% decline in opioid mortality through a multi-faceted program that included an increased capacity "hub" (the County) and increased number of physicians treating opioid addiction (the "spokes"); a Safe Recovery syringe exchange center and low-barrier sites for buprenorphine treatment; and support for a recent statute requiring such medications to be provided to prisoners with addiction treatment.[367]

iii. As noted in the *New England Journal of Medicine* in 2010, prescription opioids are "essentially legal heroin." In a comment as to how the FDA should revise a Risk Evaluation and Management Strategy (REMS) for use of opioids, a FDA Advisory Board member stated, "We need to think about how we would construct a REMS if we were going to be marketing heroin."[368] I agree with these statements, since prescription opioids are as addictive as heroin and operate on the same neuro-circuitry in the same

[365] *Id.*
[366] *Id.*
[367] City of Burlington, Mayor's Office, Press Release, "Mayor Miro Weinberger and Community Partners Announce 50 Percent Decline in Opioid-Related Overdose Fatalities in Chittenden County in 2018 (February 14, 2019). See https://www.burlingtonvt.gov/Press/mayor-miro-weinberger-and-community-partners-announce-50-percent-decline-in-opioid-related.
[368] Okie S. A flood of opioids, a rising tide of deaths. *N Engl J Med*. 2010;363(21):1981-1985. doi:10.1056/NEJMp1011512, at p. 1981.

manner. Current REMS training is insufficient to educate prescribers about the risks of opioids. We need more comprehensive prescriber training on the evidence of benefits and harms with opioids for medical use, how to monitor patients taking opioids for medical use, how to taper patients off opioids, and how to intervene when a problem arises.

iv. Medical and nursing schools across the country are beginning to implement addiction medicine curricula, an essential part of the reform process to combat this epidemic. I have led an initiative here at Stanford University School of Medicine to create our first ever addiction medicine curriculum since 2017, and I am involved in promoting similar initiatives across the country.

A. I testified at a White House symposium[369] on the importance of educating health care providers on addiction treatment and safe prescribing. At that symposium, I suggested a school loan repayment program to incentivize health care providers to treat addiction in underserved areas after completing their training. This suggestion was taken up by Representative Clark and Representative Rogers as the Substance Use Disorder Workforce Loan Repayment Bill, which was included as a key provision in the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act, also known as the SUPPORT Act, passed September 28, 2018. Although the legislation was approved, there is yet to be a source of funding.

B. I am the Program Director for Stanford's Addiction Medicine Fellowship, a one-year fellowship to provide advanced training in addiction medicine. I also work on a national level to promote these fellowships, and was the inaugural president of the Addiction Medicine Fellowship Directors' Association (AMFDA).

C. I have authored articles on the importance of teaching addiction medicine to medical students, residents, and fellows, including "The Opioid Epidemic as a Watershed Moment for Physician Training in Addiction Medicine" (Academic Psychiatry, 2018)[370] and "Qualitative

[369] The Addiction Medicine Foundation, "Congressional Briefing – Addiction Medicine: The Urgent Need for Trained Physicians" (September 28, 2017), see https://www.youtube.com/watch?v=y6kBoQckmHw

[370] Lembke A, Humphreys K. The Opioid Epidemic as a Watershed Moment for Physician Training in Addiction Medicine. *Acad Psychiatry*. 2018;42(2):269-272. doi:10.1007/s40596-018-0892-8.

Assessment of Clerkship Students' Perspectives of the Topics of Pain and Addiction in their Preclinical Curriculum (Academic Psychiatry 2018).[371] In these articles, I address the need for more robust training in the screening and intervention of patients with the full spectrum of opioid use disorders (including misuse and dependence). I further recommend increasing medical school hours of training in addiction medicine, including safe prescribing of controlled substances.

v. Consider prohibiting the pharmaceutical industry from funding or influencing Continuing Medical Education (CME) courses for prescribers.

vi. Consider promoting CME education which explicitly eschews industry funds and influence, and providing academic detailing (unbiased, evidence based information for prescribers).

vii. Earmark money to provide medical school, residency, and fellowship training in addiction treatment.

b. Secondary prevention: limit progression of harm by helping patients on dangerously high doses come down or off of opioids, independent of whether they are addicted, and by implementing harm reduction strategies to mitigate the dangers of opioids.

i. To accomplish effective, safe, and compassionate opioid tapers in this country, we need funding to build de-prescribing clinics to provide treatment for opioid dependent patients. Where de-prescribing clinics are not feasible, we need to embed an interdisciplinary, chronic care treatment team inside of primary care to support deprescribing/opioid tapering. This chronic care team would consist of physicians, nurses, social workers, case workers, psychologists, and others trained to help patients manage the physically and emotionally taxing process of decreasing prescribed opioids. Primary care doctors, already overloaded with responsibilities, are unlikely to achieve successful tapers in opioid dependent, high dose legacy patients, without significant incentives and support. This will require an enormous investment of resources, as it is estimated that millions of Americans are dependent on opioids and suffering from or at heightened risk for adverse consequences.

[371] Raber I, Ball A, Papac J, Lembke A, *et al.* Qualitative Assessment of Clerkship Students' Perspectives of the Topics of Pain and Addiction in their Preclinical Curriculum. *Acad Psychiatry*. 2018;42(5):664-667.

ii. I worked with colleagues at Stanford to develop a protocol for helping opioid dependent patients compassionately and safely taper down or off of prescribed opioids: "The BRAVO Protocol." The protocol has been adopted by the Oregon Pain Guidance, the Oregon Pain Task Force, and has influenced other opioid task forces around the country who are struggling with the problem of opioid dependent (but not addicted) chronic pain patients.[372]

iii. We have created a free online continuing medical education course - "The BRAVO Protocol: How to Taper Patients Off of Chronic Opioid Therapy." This course, created in conjunction with the Stanford continuing medical education office, teaches prescribers how to safely and compassionately taper opioids, something that is not currently taught in medical schools.

iv. The course has been positively featured in the lay press, highlighting that the course features the first-person account of a patient who was, with support, able to taper off of opioids and experienced improved chronic pain as a result.[373] We have created a companion page summarizing The BRAVO Protocol, which has gained wide informal distribution among prescribers. It summarizes the key learning points as below. (See BRAVO Protocol summary attached to this report.) The bottom line is, helping patients to decrease or discontinue long term opioid therapy presents a challenging clinical scenario, especially in patients on high doses (greater than 80 MEDs), with moderate to severe chronic pain, and co-occurring mental health disorders (depression, anxiety, PTSD). For this type of complex chronic pain patient, the usual recommendation to decrease opioids by 10% of the starting dose every week frequently will not apply. These patients often need slower tapers on the order of 5-10% decreases or less every month. Expert consensus suggests the taper speed should be tailored to the individual needs of the patient. Some patients who have been on opioids for years to decades, may require *years* to taper their dose. With this complex chronic pain patient in mind, the BRAVO protocol outlines a safe and compassionate strategy to approach opioid tapering, while also maintaining a therapeutic alliance between the treatment team and each patient.

[372] Oregon Health Authority Oregon Opioid Taper Guidelines Task Force Resources. See https://www.oregon.gov/oha/PH/PREVENTIONWELLNESS/SUBSTANCEUSE/OPIOIDS/Documents/taskforce/tapering-taskforce/2019-Opioid-Taper-Task-Force-Resources.pdf.

[373] Parloff R. Tapering off long-term Rx opioids: a first-hand account, Opioid Institute. (October 15, 2018) See https://opioidinstitute.org/2018/10/15/tapering-opioids-lembke/.

v. Other harm reduction strategies include increasing naloxone distribution, promoting clean needle exchanges, improving patient education regarding safe medication storage and appropriate disposal of excess medications, and increasing public awareness of poison center services.

c. Treatment

i. We need a robust infrastructure to treat addiction, inside and outside of medicine. Such an infrastructure does not currently exist. Instead what we have are siloes of care with limited and contingent funding, or treatment centers accessible only by the rich.

ii. Addiction treatment should be offered within every hospital, clinic, emergency room, jail, drug court, etc., across America. 'Meeting patients where they are' has become a mantra for the field. Patients with this complex behavioral illness are more likely to engage in treatment when they are offered treatment in settings where they are frequently found, like in hospitals, emergency rooms, jails, and even in settings where they might be using drugs (such as at the site of first responders, clean needle exchange sites, safe consumption sites, etc.).

iii. An effective addiction treatment infrastructure should be based on evidence-based treatments for addiction, including buprenorphine, methadone maintenance, and naltrexone. Opioid agonist therapy (buprenorphine or methadone maintenance) has one of the most robust evidence bases of any addiction treatment. Multiple placebo controlled trials over many decades have demonstrated the efficacy of opioid agonist therapy in the treatment of opioid use disorder.[374]

iv. Addiction is a chronic relapsing and remitting disorder, requiring a chronic care model and a team based approach, including a peer recovery coach, care coordinator, behavioral health specialist, licensed counselor, and a primary care professional.[375] One way to address this problem within our current health care system, is to co-locate behavioral health specialists within primary care, or create a hub and spoke model with specialty clinics providing support to primary care clinics. A concurrent strategy is to build Centers of Excellence for Addiction Treatment at every major

[374] Strang J, Babor T, Caulkins J, Fischer B, Foxcroft D, Humphreys K. Drug policy and the public good: evidence for effective interventions. *Lancet*. 2012;379(9810):71-83, at p. 78.
[375] "The Addiction Recovery Medical Home As An Alternative Payment Model," Health Affairs Blog, December 12, 2018. DOI: 10.1377/hblog20181211.111071. *Heal Aff Blog*. doi: 10.1377/hblog20181211.111071, at p. 3.

medical center around the country, similar to existing Centers of Excellence for cancer, cardiac disease, and diabetes.

v. As a chronic illness, addiction can require lifelong treatment. In my clinical experience, most people with moderate to severe opioid use disorder struggle to some degree to remain abstinent for the rest of their lives and there is a high rate of relapse when individuals go off of MAT treatment. Thus, the abatement plan to address the opioid epidemic should focus on providing the maximum level of both MAT and non-MAT treatment resources possible, as quickly as possible, and should maintain this level of treatment through at least 2034, as contemplated in the proposed abatement plan.

vi. A successful treatment system would allow for those with the disease to titrate their treatment based on illness severity over time, with the recognition that the normal course of addiction involves periods of remission and recurrence, just like cancer.

vii. Addiction treatment and recovery requires intensive individual and/or group therapy interventions, which should be integrated into treatment alongside medications.

viii. Mutual help groups such as Narcotics Anonymous have a long tradition of aiding people with addiction achieve and maintain recovery. New models employing peer counselors as part of an interdisciplinary medical team to treat and target addiction, are being investigated. These models should be considered as a way to bridge inpatient and outpatient treatment and sustain recovery as patients return to their normal lives. Undergirding the creation of a robust infrastructure to target and treat addiction, is the need for a trained workforce to deliver this care. In Ohio, Office-Based Opioid Treatment on buprenorphine products has steadily increased, from 12,089 patients in 2008, to 67,665 in 2017.[376]

17. With an aggressive infusion of resources and efforts in Summit and Cuyahoga counties, it would be reasonable that within four years the number of bellwether individuals with OUD who receive substance abuse treatment services within a year could double, assuming that only 20% of individuals with OUD currently receive treatment. Note: 20% estimate based on SAMHSA: "Only 20% with OUD received specialty addiction treatment"[377]

[376] Rick Massatti, Treatment Options for Opioid Use Disorder in Ohio. Ohio Mental Health and Addiction Services. 28th September 2018. Presented. At slide 8.

[377] Substance Abuse and Mental Health Service Administration, "SAMHSA/HHS: An Update on the Opioid Crisis", March 14, 2018, at p. 2. See https://www.samhsa.gov/sites/default/files/aatod_2018_final.pdf

18. With an aggressive infusion of resources and efforts in these two counties, it would be reasonable that within four years the percentage of bellwether individuals with OUD who receive MAT could quadruple from approximately 7% of individuals with OUD currently to approximately 28% of individuals with OUD. Note: 7% estimate based on assumption that 1/3 of individuals receiving treatment also receive MAT. Corresponds to national figures that less than 10%with OUD receive MAT.[378]

a. Once the populations receiving treatment/MAT are increased as described above, it would be necessary to provide treatment at those same levels for the foreseeable life expectancy of the patients, because OUD is a disease with constant risk and high rate of relapse and remission.

b. If the treatment rates described above are achieved, there would be a large impact on deaths and other outcomes, as evidenced by the experience in Massachusetts and Vermont, described above. The mix of MAT that is buprenorphine and naltrexone-based will continue to increase relative to methadone-based

D. Conclusion:

The ongoing epidemic of morbidity and mortality due to prescription opioids is the result of aggressive marketing and promotion of such drugs, and in particular the overstatement of benefits and understatement of harms. Opioid manufacturers engineered the increase in opioid prescribing by directly targeting doctors, by promoting key opinion leaders, by infiltrating continuing medical education courses, by supporting professional medical societies, and by co-opting medical watchdog organizations like *The Joint Commission*, to convince prescribers that liberal opioid prescribing is based on science. In fact there has never been sufficient evidence to justify widespread use.

Authoritative reviews have concluded that the evidence of benefits for chronic pain is "weak," "inconclusive," and "insufficient to assess effects on health outcomes." Defendants' clinical trials were too short to provide reliable evidence of long-term benefit, especially in light of highly selected populations and substantial rates of attrition from the studies. As shown by the SPACE trial, a gold standard, long-term study by independent researchers, non-opioids are as good or better than opioids for chronic pain, and have fewer side effects. On the risk side, Defendants claimed that addiction was "rare," "uncommon," or "less than 1%," based on inapplicable data from non-comparable populations. The true rate of addiction in a clinical population is probably closer to 21-29%, across the full spectrum of OUD. In addition, there are millions of patients today who are physiologically dependent on opioids, unable to reduce their doses, and left to suffer the risks and consequences of long-term opioid therapy.

Ending the epidemic of opioid addiction, dependence, and death will require significant investment of resources. An effective strategy will be multifaceted, and will accomplish the

[378] Sandoe, E., *et al.*, "Policy Levers That States Can Use to Improve Opioid Addiction Treatment And Address the Opioid Epidemic", Health Affairs Blog. (Oct. 2, 2018). See https://www.healthaffairs.org/do/10.1377/hblog20180927.51221/full/

following: prevent new cases of addiction, dependence, and other related harms (primary prevention), limit progression of harm (secondary prevention), and treat existing cases (treatment). In a *New England Journal of Medicine* commentary regarding the CDC Opioid-Prescribing Guideline, CDC physicians Thomas Frieden and Debra Houry stated, "We know of no other medication routinely used for a nonfatal condition that kills patients so frequently."[379]

Dated: March 25, 2019

Anna Lembke, M.D.

[379] Frieden TR, Houry D. Reducing the Risks of Relief — The CDC Opioid-Prescribing Guideline. *N Engl J Med*. 2016. doi:10.1056/nejmp1515917, at p. 1503.

Anna Lembke, M.D. Report

APPENDIX I

I.A: Purdue Pharma

I.B: Mallinckrodt

I.C: Janssen

I.D: Endo Pharmaceuticals

I.E: Allergan

Anna Lembke, M.D.

Appendix I.A.: Purdue Pharma

Purdue Misleading Messaging

A. Benefits of Opioids Not Supported by Reliable Scientific Evidence

1. "Opioids are effective for chronic pain"

- "[W]e now know that many patients with chronic, nonmalignant pain respond very well to opioids and that, contrary to our teaching, addiction is very rare and possibly nonexistent as a result of treating such patients with opioids. The barriers to vastly improved treatment for hundreds of thousands of people in pain, are simply the misinformation and prejudice of doctors, pharmacists and regulatory bodies." Purdue Physicians' Pain Management Speaker Training Program, April 18-20, 1997. PKY181654940-PKY181654982 at 4966.

  Comment: This quote summarizes the essential message promoted initially by Purdue and subsequently by other opioid sellers: that opioids are effective for chronic pain, and that "addiction is very rare and possibly nonexistent," as a result of such treatment. With some variation, the promotional messages detailed in this appendix follow those two themes. As to the claim of efficacy for chronic pain, there was not then, and there has never been, reliable evidence to support the claim (Report, Section C4); as to the assertion of "rare" addiction risk with opioid therapy, there were numerous studies that had reported a range of addiction as high as 24% before the opioid sellers began the aggressive marketing campaign that omitted any reference to those data, and numerous additional, subsequent studies consistent with the earlier results, (Report at section C5).

- "Opioid analgesics are indicated for moderate to severe pain that cannot be relieved with other agents. Opioids are effective, easily titrated, and have a favorable benefit-to-risk ratio. Large doses of opioids may be needed to control pain if it is severe, and extended courses may be necessary if the pain is chronic. Tolerance and physical dependence are normal physiologic consequences of extended opioid therapy and must not be confused with addiction. Patients and family members must be educated regarding the difference between tolerance, physical dependence, and addiction. Patients with chronic, severe pain must not consider themselves addicts because they are being treated with opioids. Concerns about addiction should not prevent the appropriate use of opioids. McPhee JS, Schroeder SA. In Lange's Current Medical Diagnosis Treatment, 1996 p 13." Purdue Physicians' Pain Management Speaker Training Program, April 18-20, 1997. PKY181654940-PKY181654982 at 4969.

Comment: This quote builds on the basic message (above) by recommending titration to "large doses," without disclosing that risk goes up as dose goes up; and by downplaying the significance of physical dependence, which is a significant medical problem. (Report at section C6).

- Presentation by Dr. Melvin Gitlin entitled "The Use Of Opioids in the Treatment of Chronic Non-Cancer Pain" at the Purdue Physician's Pain Management Speakers Training Program, November 5-7, 1999. PKY181655140-PKY181655233 at 5155-5157 in which he states, "Historically the use of opioids for pain management has been influenced less by scientific data than by subjective attitudes, personal opinion and legislative regulatory influence….Regulatory agencies in the United States are increasingly acknowledging this; some are seeking to reassure clinicians that the legitimate use of opioids should not engender fear of reprisal…. A well designed, double-blind, randomized cross over trial utilizing patient controlled analgesia morphine studied opioid responsiveness in chronic pain. The authors demonstrated that although nociceptive pains exhibited a better analgesic response than did neuropathic pain, approximately 50% of patients with neuropathic pain did show a good or better analgesic response to the opioid." The study to which Dr. Gitlin refers, by Jadad, et al, "Morphine responsiveness of chronic pain", Lancet 1992, is not in fact a study of the use of long term opioid therapy in the treatment of chronic pain. Rather it is a study of one-day dosing of opioids in a population of patients with chronic pain, answering an entirely different question than whether opioids work for the treatment of chronic pain. Treating chronic pain patients for a day is not comparable to treating the same population with opioids on a long-term basis.

- Presentation by Dr. Mary Stegman entitled "Pain Management in the Elderly Patient, Special Considerations," for Purdue's Physician's Pain Management Speakers Training Program, November 5-7, 1999. PKY181655140-PKY181655233 at 5168, in which she states "opioid analgesic drugs are effective for moderate to severe pain," under the heading "AGS Clinical Practice Guidelines for Chronic Pain," without clarifying the lack of reliable evidence for the use of opioids in the treatment of chronic pain.

2. Opioids are first-line treatment for all types of pain

- "Opioids are our strongest and safest medications for most disablingly-severe pain. Our obligation is to consider them in all such cases." "Control of Pain: Every Person's Right " Pain Management Speaker Training Program for Physicians, May 5-7, 2000. PKY180170528-PKY180170653 at 0545. Part of a Purdue sponsored speakers training program in Beverly Hills, CA.

- "Opioids for Neuropathic Pain--All patients & all types of pain are opioid responsive. There can be variation in the degree of response. May need to titrate

to adequate analgesia but intolerable side effects; change opioids. Nociceptive (visceral, somatic) and neuropathic pain responsive to opioids." HSS Training Presentation, August 25, 2000. PKY180435433-PKY180435707 at 5565. Purdue sales reps are called "Health Systems Specialists" (HSS) and this was a Purdue Training Presentation for Reps and District Managers.

Comment: The quotes above do not distinguish between acute pain and chronic pain. While there was reliable evidence of efficacy of opioids for acute pain, as noted above and in the Report, there was no reliable evidence of efficacy for chronic, non-cancer pain. It was misleading to make a blanket statement of efficacy without making this distinction clear.

3. Opioids are safer than the alternatives

- "We now know that in appropriately selected patients, opioids have a low morbidity (perhaps less than NSAIDS), and a low addiction potential. Although tolerance may occur in some cases, generally patients become tolerant to bothersome side effects more so than to analgesic effects. Evidence from cancer studies suggests that when patients clinically stable on a certain opioid dose, request a dose escalation, it may be more related to progression in their disease than to tolerance." Physicians' Pain Management Speakers Training Program, March 20-22, 1998. PKY181655057-PKY181655139 at 5092.

- Presentation by Dr. Mary Stegman entitled “Pain Management in the Elderly Patient, Special Considerations,” for Purdue’s Physician's Pain Management Speakers Training Program, November 5-7, 1999. PKY181655140-PKY181655233 at 5166, in which she highlights the risks of acetaminophen, including renal and hepatotoxicity, and in which she claims opioids are “safer than NSAIDS,” but never discusses the absolute or relative risks of opioids.

  Comment: There was no reliable evidence to claim that opioids were “safer, or “perhaps” safer than NSAIDs or acetaminophen. As to NSAIDs, the best available evidence shows that opioids confer greater risk of mortality and adverse events. (Solomon study, Report at section C4.); also, the Krebs study (SPACE trial) (Report at section C4) found more adverse events in the opioid group than among the non-opioid group that consisted of acetaminophen and NSAIDs, with a small percentage of patients on tramadol.

4. Opioids improve function and quality of life

- "In studies of patients with non-malignant pain...Rapid reduction in pain intensity over the first 24 hours; By day three, patients had achieved 94% of their total pain reduction; Patients reported improved ability to sleep, walk, perform normal work, get along with other people, enjoy life." OxyContin Launch Plan, September 27, 1995. PURCHI-003286781-PURCHI-003286881 at 6804.

- "Provides quality of life benefits-relative to placebo, OxyContin significantly decreased pain, and improved quality of life, mood and sleep." OxyContin Advertising and Black Box Warnings, June 15, 1998. PKY180625450-PKY180625745 at 5455

- "Controlled-release opioids - Cognitive Effects: decreases anxiety, decreased hostility, no declines in cognitive function, improved psychomotor speed, improved sustained attention." Physician's Pain Management Speakers Training Program, November 5-7, 1999. PKY181655140-PKY181655233 at 5175.

- "Benefits of Long acting opioids -- Better pain reduction with better function. Improved sleep. Reduced anxiety. Reduced hostility. No impairment of cognitive function. Improved psychomotor speed. Improved sustained attention." HSS Training Presentation, August 25, 2000. PKY180435433-PKY180435707 at 5635.

  Comment: The statements above are misleading because they were intended to justify long-term OxyContin therapy for chronic pain, based on short-term studies.

5. Not using opioids is tantamount to undertreating pain, is hence immoral, may make pain worse in the long run, and risks reprisal from regulatory bodies.

- Presentation by Dr. Neil Irick entitled “Can We Justify Undertreating Pain?” for Purdue’s Physician's Pain Management Speakers Training Program, November 5-7, 1999 in which he invokes The Joint Commission Requirements as justification and persuasion: “The patient’s right to pain management is respected and supported,” “Pain as the 5th vital sign,” “Statement of patient rights available to all.” Dr. Irick also states, “Remember: resolve that no patient should suffer needlessly, listen to the patient, believe the patient, document, be your patient’s advocate.” PKY181655140-PKY181655233 at 5150 and 5152

- Presentation by Dr. Mary Stegman entitled “Pain Management in the Elderly Patient, Special Considerations,” for Purdue’s Physician's Pain Management Speakers Training Program, November 5-7, 1999. PKY181655140-PKY181655233 at 5161 in which she states, “In 2000, JACHO will demand pain TX [treatment].”

- "Based on new literature on the Pathophysiology of pain, it is important to PREVENT the pain as opposed to simply treating the pain. Otherwise, you could have patients develop what is referred to as ‘Wind up’ which can lead to a complex pain syndrome. Let's say you had a patient present with low back pain from lifting heavy boxes. When that patient lifted the boxes and the injury occurred, the C fibers in his body were stimulated and started firing pulses basically like a strobe light. Those fibers synapsed with the secondary neurons

and carried the pain signals to the brain. Think of the secondary neurons like the aperture of a camera, except that instead of the aperture closing when that strobe light hits it, the aperture actually opens. The more light/or stimulus that spills through the aperture, the greater the sensation of pain. So, what happens is even though that stimulus may be diminishing, the threshold for pain has been lowered, and the number of signals have actually increased. This whole process starts a CASCADE OF EVENTS because once these signals are recognized on a consistent basis, they turn on the NMDA receptors which then release prostaglandins and nitric oxide initiating the ENTIRE chain of events again in the adjacent neurons. And what that does is lowers the threshold for pain again, and they start firing spontaneously. UNTIL these pain signals can be turned off the patient will remain in this 'wind up mode' and could develop a complex pain syndrome." HealthSouth Pain Management Plan, April 19, 2001. PKY181246683-PKY181247419 at 6851. Document is part of "OxyContin Files (HD)" which includes presentations and papers made by Purdue to HealthSouth re: adoption of their new pain management plan.

Comment: The statements above were misleading and detrimental to patients, for the following reasons. First, these statements represent the opioid sellers' efforts to increase prescribing by instilling fear of reprisal from the State Medical Boards and/or The Joint Commission, as well as patients demanding opioids and complaining about their care. The message to prevent pain before it happens was leveraged to support the controversial idea that untreated pain can lead to centralizing pain disorders, which would not only leave acute pain untreated, but also risk a life-time condition if a centralizing pain disorder were to develop. Even if this centralizing pain phenomenon exists, opioids are the worst possible treatment, because these disorders are closely linked to depression and addiction, and the risks for such conditions are exacerbated by opioid therapy.

B. Risks of Opioids Understated

1. Addiction is rare

- "Realize that drugs and doctors do not cause drug addiction. Admit that withholding pain medication can be deleterious. Admit that true addiction is much less of a problem than presumed." Purdue Physicians' Pain Management Speakers Training Program, March 20-22, 1998. PKY181655057-PKY181655139 at 5080.

- Presentation by Dr. Melvin Gitlin at the Purdue Physician's Pain Management Speakers Training Program, November 5-7, 1999. PKY181655140-PKY181655233 at 5156, in which he states, "Persuasive evidence that the use of opioid presents either a risk to the health of the individual or to society is lacking. Similar prejudices had been advocated to impede the opioid treatment of patients with malignant pains and are being overcome."

- Presentation by Dr. Mary Stegman entitled “Pain Management in the Elderly Patient, Special Considerations,” for Purdue’s Physician's Pain Management Speakers Training Program, November 5-7, 1999. PKY181655140-PKY181655233 at PKY181655169, in which she states "Myth: Opiates create addicts” outlining a study of 10,000 burn patients, 0 patients (0.00%) were addicted; another study of 25,000 patients, only 7 patients (0.03% patients) were addicted, concluding “Forget That Excuse!'" As discussed in my Report, the studies to which she refers are non-representative samples in studies ill-designed to assess for misuse and addiction.

2. The problem is the ‘addicts,’ not the drug

- "Are Opioids Always Addictive? No! Watch out for cherry syrup addicts! Opioid addicts should not be given opioids without careful consideration of the circumstances." Accredited Pain Management Program for the Educator, April 3-6, 2000. PKY180775599-PKY180775707 at 5650

  Comment: By using the term “cherry syrup addicts,” the author is presumably referring to patients with opioid addiction getting treated with methadone in liquid form from a methadone maintenance clinic. This pejorative usage is typical of the ways in which Purdue labeled and stigmatized people with opioid use disorder, and promoted the idea that by separating opioid addicted persons as a distinct population, the remaining patients could be prescribed opioids without risk.

- “Molecules don’t hook patients, patients with psychopathology take drugs to be fixed. Addicts want medications for wrong reason, trying to get high, not to have less physical pain.” Accredited Pain Management Program for the Educator, April 3-6, 2000. PKY180775599-PKY180775707 at 5652

  Comment: This statement perpetuates the myth that ‘addicts’ are a separate category from ‘legitimate’ pain patients. The reality is that legitimate pain patients can and do get addicted through an opioid prescription.

3. No dose is too high; optimal dose is determined by titrating upwards until analgesia

- "No ‘ceiling’ to analgesic efficacy - may be titrated upward as necessary. With full agonists, such as oxycodone, ‘effectiveness with increasing doses is not limited by a 'ceiling'’." OxyContin Launch Plan, September 27, 1995. PURCHI-003286781-PURCHI-003286881 at 6804.

- "No maximum daily dose or ‘ceiling’ to analgesic efficacy. May be titrated every 1 to 2 days, if necessary. Common opioid side effects may be effectively managed- many, except constipation, diminish over time for most patients."

OxyContin Advertising and Black Box Warnings, June 15, 1998. PKY180625450-PKY180625745 at 5452.

- Presentation by Dr. Mary Stegman entitled “Pain Management in the Elderly Patient, Special Considerations,” for Purdue’s Physician's Pain Management Speakers Training Program, November 5-7, 1999. PKY181655140-PKY181655233 at 5172, in which she states “Titrate to effectiveness not to milligrams.”

- "There are no standard opioid doses. Patients experience their pain uniquely. Dosages not consistent due to individual variations in pain intensity mechanisms of action. Patients need doses that relieve or modify the pain without toxicity. Milligrams Just Don't Matter...Milligrams are not the issue, pain control and absence of toxicity are the issues." Accredited Pain Management Program for the Educator, April 5, 2000. PKY180775599-PKY180775707 at 5647.

  Comment: The statements above are misleading because they omit that increased dose increases risk of dependence, addiction, and numerous adverse effects, including death.

4. Dependence is not a significant problem and is easily reversible; false analogy with insulin

- "Now, when was the last time that you took a patient off insulin because their blood sugar had gotten to normal? Do you taper your patients off their antihypertensive when their blood pressure gets to normal? In primary care our assumption is that we're going to be treating people with chronic diseases for long-term, so why don't we do that with pain patients?" "Legal and Ethical Issues Affecting Pain Management", © 2001 a “Free CME” course “supported by an education grant from Purdue Pharma” and distributed by FamilyPractice.com and Purdue.. PKY180769094-PKY180769535 at 9123 and 9095

  Comment: Comparing opioids to insulin is a false analogy because insulin does not cause diabetes; whereas exposure to opioids causes opioid dependence, and in a subset, opioid addiction.

- "Addiction is a behavioral disorder of 'compulsive drug use, despite harm.' This has not been recorded as a result of the medical use of opioids. Opioids do cause physical dependence, i.e. there is a brief, flu-like withdrawal syndrome on suddenly stopping them. But this is not addiction, it is not dangerous and is easily avoided by tapering opioids over about 2 weeks. (By contrast, the withdrawal syndrome for benzodiazepines can be very dangerous, and very prolonged. Preventing it may require tapering over a period of several months.)" Purdue Physicians' Pain Management Speaker Training Program, April 18-20, 1997. PKY181654940-PKY181654982 at 4966.

- Presentation from Dr. Neil Ellison at the Purdue's Physicians Pain Management Speakers Training Program in San Antonio, Texas on April 19, 1997: "Physical dependence will occur in most patients regularly taking opioids for prolonged periods of time (usually great than several weeks); however, if the cause of the pain is relieved, these patients can safely and rapidly be withdrawn completely by fractionating (usually by 1/3-1/2 their doses daily or every other day). The patient can usually discontinue completely without withdrawal symptoms…" PKY181654940-PKY181654982 at 4950.

  Comment: Dependence and tolerance are serious physical conditions in themselves; they also lead to increased doses and addiction in a subset of patients, and to long, slow, and often failed attempts at tapering.

5. Tolerance is rare: respond with higher dose

- "(Despite different findings in experimental animals), a remarkable phenomenon is observed in the clinical setting. Loss of analgesia rarely occurs in patients with stable pain syndromes. Patients without progressive disease…typically achieve stable dosing that extends for a prolonged period. When the need for dose escalation occurs, an alternative explanation, typically worsening of the underlying disease, can usually be identified." Physicians' Pain Management Speaker Training Program, April 18-20, 1997. PKY181654940-PKY181654982 at 4969, quoting Portenoy RK. In "Pain Management: Theory and Practice," ed. Portenoy Kanner, FA Davis Company, 1996: Chapter 11, p255.

- "Tolerance is defined as the need for increasing doses of medication to maintain the same effect. This is easily and reliably produced in animal models, yet is rarely seen in humans. In fact, in the case of cancer pain, what has thought to be tolerance has been shown to typically be disease progression necessitating the need for increased opioids to maintain comfort." Purdue Physicians' Pain Management Speaker Training Program, presentation by David Haddox April 18-20, 1997. PKY181654940-PKY181654982 at 4962.

- "Although tolerance may occur in some cases, generally patients become tolerant to bothersome side effects more so than to analgesic effects. Evidence from cancer studies suggests that when patients clinically stable on a certain opioid dose, request a dose escalation, it may be more related to progression in their disease than to tolerance." Physicians' Pain Management Speakers Training Program, March 20-22, 1998. PKY181655057-PKY181655139 at 5092.

  Comment: Tolerance is not "rare" in humans. It is common. Tolerance leads to increased dosage and increased risk.

6. Pseudo-addiction – respond with more opioids

- "[I]n the setting of undertreated pain, some patients develop aberrant behaviors that may be quite similar to those associated with addiction. When pain is relieved, the behaviors cease and opioids and other drugs are used responsibly." Physicians' Pain Management Speakers Training Program, March 20-22, 1998. PKY181655057-PKY181655139 at 5100.

- Types of Pseudoaddiction Behavior: "Hoarding; Concern about supply; May be going to multiple physicians and pharmacies; Drug-seeking behaviors common; First described in cancer patients." Physicians' Pain Management Speakers Training Program, March 20-22, 1998. PKY181655057-PKY181655139 at 5081.

- "Pseudoaddiction: appropriate drug seeking behavior demanding doses before they are scheduled; viscous cycle of anger, isolation, and avoidance leading to complete distrust. Weissman DE, Haddox DJ. Pain 1989;36:363-6. Increase the opioid dose by 50%, assure that breakthrough doses are available; complaints resolve when analgesia is established." Physician's Pain Management Speakers Training Program, November 5-7, 1999. PKY181655140-PKY181655233 at 5208. Haddox is now a Purdue Pharma VP of Health Policy. See Haddox ResearchGate Profile page at <https://www.researchgate.net/profile/J_Haddox> Accessed on January 25, 2019.

- "Pseudoaddiction Relative to Psychiatric Pain Consultations--Involves appropriate attempts to obtain medication to relieve pain. "Clock watching" behavior is indicative of under treatment of pain. We should believe patients unless evidence proves otherwise. Consider 50 to 100% dose increase to see if the behavior changes." Accredited Pain Management Program for the Educator, August 5, 2000. PKY180775599-PKY180775707 at 5649.

- "...the more the patient insists on the need for stronger pain medicine, the more likely we are to withhold analgesia, on the grounds that this insistence shows 'substance abuse' for which the treatment is abstinence from the 'offending substance'. We equate this 'drug seeking behavior' with addiction, and use it to justify further undertreatment or even complete withdrawal of analgesics. This further reinforces the patient's desperate pursuit of pain relief. If this leads to manipulativeness or frank deceit, the misdiagnosis of addiction is reinforced. Not only the doctors, but also the patient and family may conclude that the problem is drug addiction. This is called 'pseudo-addiction,' a term first defined by Weissman and Haddox." From presentation "Control of Pain: Every Person's Right "," Pain Management Speaker Training Program for Physicians, May 5-7, 2000. PKY180170528-PKY180170653 at 0545.

- "The distinction can usually be made quite simply. For a period of about a week, prescribe a substantially increased dose of opioid, preferably with a range of doses so that the patient can explore the optimum dose. The aim is to challenge the patient's ability to shed drug-seeking behavior when adequate analgesics are available. Every day the patient records pain level, activities tolerated, and total pills taken. After a week, he/she brings the record to the physician, along with remaining pills. Ideally the partner should come also. lf the problem is pseudoaddiction, the patient will be visibly more comfortable and refreshed; the partner will corroborate the patient's account of improved activity tolerance; the daily pill count will be medically credible; and the remaining pill count will fit with the record. None of the aberrant behaviors listed above will have occurred: drug-seeking behavior has been extinguished at a stroke." From "Control of Pain: Every Person's Right" presentation, Pain Management Speaker Training Program for Physicians, May 5-7, 2000. PKY180170528-PKY180170653 at 0545.

  Comment: As detailed in the Report at section C7, pseudo-addiction is not a reliable diagnosis; the term pseudo-addiction was developed by a physician (Haddox) who became an executive at Purdue, and a review article found that impartial scientists criticize its usage, whereas authors affiliated with the opioid sellers advocate the concept.

Report of Anna Lembke, M.D.

Appendix I.B: Mallinckrodt Promotional Messages

Mallinckrodt Misleading Messaging

A. Benefits of Opioids Not Supported by Reliable Scientific Evidence

1. Opioids are effective for chronic pain

- "It is currently recommended that every chronic pain patient suffering from moderate to severe pain be viewed as a potential candidate for opioid therapy." Date: 2012. Source: Mallinckrodt promoted a book through C.A.R.E.S. Alliance: Defeat Chronic Pain Now! at p. 174, http://defeatchronicpainnow.com/.

- "Studies have shown that many chronic pain patients can experience significant pain relief with tolerable side effects from opioid narcotic medication when taken daily and no addiction." *Id.* at p. 178.

  Comment: These quotes summarize the essential message promoted initially by Purdue and subsequently by other opioid sellers: that opioids are effective for chronic pain, and that "addiction is very rare and possibly nonexistent," as a result of such treatment. With some variation, the promotional messages detailed in this appendix follow those two themes. As to the claim of efficacy for chronic pain, there was not then, and there has never been, reliable evidence to support the claim (Report at section C4); as to the assertion of "rare" addiction risk with opioid therapy, there were numerous studies that had reported a range of addiction as high as 24% before the opioid sellers began the aggressive marketing campaign that omitted any reference to those data, and numerous additional, subsequent studies consistent with the earlier results. (Report at section C5.)

- Opioids are "Recognized as effective," MNK-T1_0001279950, at *8 (produced natively), [citing Chou, et al., "Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain." *J. Pain* 2009; 10:113-130];"Opioids are vital to the treatment of chronic pain." August 15, 2010 MNK-T1_0001279950, at *56 (produced natively).

  Comment: Mallinckrodt/C.A.R.E.S. Alliance held a "Train-the-Trainer" event on August 14-15, 2010 at the Hyatt Regency Scottsdale at Gainey Ranch, Arizona. The presentation provided training to physicians to become "Speakers" on behalf of Mallinckrodt and its hydromorphone opioid product, EXALGO, based on the instruction they received at the event. The presenters included Jeffrey Gudin, MD, and Steven Passik, MD, both of whom had received financial support from opioid sellers. The Agenda at MNK-T1_0006127321- MNK-

T1_000612783, at 7322-7323 includes Passik's "Education" module. The slides are misleading because the Chou article cited in the presentation does not mention that the Guidelines in that article relating to initiation of chronic opioid therapy, titration, etc. are based on "Low Quality Evidence," which the article defines as follows: "**Low-quality**: **Evidence is insufficient to assess effects on health outcomes** because of limited number or power of studies, large and unexplained inconsistency between higher quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes." *J. Pain* 2009; 10:113-130 at 130.e5. (Emphasis added). The Mallinckrodt/Covidien "C.A.R.E.S. Alliance Train-the-Trainer" slides instructed a group of physicians to become "Speakers" who would teach other physicians that opioids were "effective" and even "vital to the treatment of chronic pain," without informing those Speakers, or those who would hear them speak, that the evidence supposedly supporting such use had been found "insufficient to assess effects on health outcomes." Mallinckrodt/Covidien provided information that was misleading and not supported by scientific evidence, in a manner intended to disperse that information to a wide audience of physicians who would be misled by the overstatement of benefits.

2. Opioids improve function and quality of life

- "[T]here is a perception that long-acting or ER opioids may permit patients to focus more on life than on pain management. For example, a longitudinal assessment of nursing home residents with persistent noncancer pain reported improvement in functional status and social engagement with long-acting or ER versus short-acting opioids. All of these potential advantages of long-acting and ER opioids may translate into improved quality of life for patients, although substantially more research is necessary to support the clinical perception that long-acting opioids are better than short-acting opioids for the management of chronic pain." Synchrony Medical - Covidien - Module 6: Opioid Treatment Landscape, 2010. MNK-T1_0001347664-MNK-T1_0001347693 at 7670-7671.

  Comment: This statement is misleading because it is intended to justify long-term opioid therapy for chronic pain, based on short-term studies.

B. Risks Understated

1. Addiction is rare

- "The bottom line: Only rarely does opioid medication cause a true addiction when prescribed appropriately to a chronic pain patient who does not have a prior history of addiction. "Date: 2012. Book is still available online. Source: Mallinckrodt promoted a book through C.A.R.E.S. Alliance: Defeat Chronic Pain Now! at p. 177 http://www.defeatchronicpainnow.com/;

https://books.google.com/books?id=VcSQGYKXWdYC&printsec=frontcover#v=onepage&q&f=false

- "Here are the facts. It is very uncommon for a person with chronic pain to become 'addicted' to narcotics IF (1) he doesn't have a prior history of any addiction and (2) he only takes the medication to treat pain. *Id.* at p. 178.

- "When chronic pain patients take opioids to treat their pain, they rarely develop a true addiction and drug craving." *Id.* at p. 176.

- "Concern about addiction can lead to: Undertreatment of pain; Inadequate pain relief; Unnecessary suffering; Increased health care costs. Opioid use disorder is 4 times higher in primary care setting of chronic pain patients (~4%)." EXALGO REMS & CARES Alliance - Train-the-Trainer - CARES Alliance Education Module - Steven Passik, PhD." August 15, 2010. MNK-T1_0001279950, at *18 (produced natively).

  Comment: These statements are misleading because they ignore the data showing addiction is common in a clinical population being treated with opioids, and because they imply that not using unproven opioid therapy is tantamount to "undertreatment of pain."

2. High risk patients can be screened and monitored to prevent addiction

- "In order to mitigate risks, its important to stratify patients according to their risk factors for abuse and addiction. Patients who are at lower risk and can usually be managed in a primary care setting are those with no past or current history of substance abuse disorder, no family history of past or current substance abuse disorder, and no major or untreated psychopathology. Patients who are at moderate risk and can be managed in a primary care setting with support from a specialist are those that may have a past history of a treated substance abuse disorder, may have significant family history of problematic drug use, or may have a past or concurrent psychopathology yet are not actively addicted. Patients who are at higher risk and can be managed by a pain specialist are those with active substance use disorder, major untreated psychopathology, or who are actively addicted." Speakers notes, "EXALGO REMS & CARES Alliance - Train-the-Trainer - CARES Alliance Education Module - Steven Passik, PhD." August 15, 2010. MNK-T1_0001279950, at *25 (produced natively).

  Comment: These statements are misleading because in fact there are no validated screening tools which can reliably predict who will and who will not get addicted to opioids through a legitimate medical prescription. It also suggests that pain specialists have more expertise in managing patients with addiction risk, when in

fact pain specialists receive as little training in addiction screening and management as most other doctors.

3. No dose is too high

- "When managing your patients' conversion to EXALGO, be sure to continue to titrate upwards until an effective dose is reached. This is essential to overall patient success. Titration should not occur more frequently than every 3 to 4 days. If more than 2 doses of supplemental medication are needed for 2 consecutive days, it may be time to titrate upward. When titrating, consider a 25% to 50% increase in dose. It may take multiple titration steps to achieve effective pain control with tolerable side effects." Exalgo Patient Identifier MSA Implementation Guide, 2014. MNK-T1_0000626241-MNK-T1_0000626269 at 6262

  Comment: The statements above are misleading because they omit that increased dose increases risk of dependence, addiction, and numerous adverse effects, including death.

4. Pseudo-addiction – respond with more opioids

- "Pseudoaddiction: Patients who are receiving an inadequate dose of opioid medications and seek more. Other behaviors less indicative of addiction: Drinking or smoking to relieve pain, expressing worry over changing to a new drug, asking for second opinion about medication, using opioids to treat other symptoms. Other behaviors more indicative of addiction: Seeing 2 doctors at once without them knowing, stealing drugs from others, selling prescription drugs." Speakers notes, "EXALGO REMS & CARES Alliance - Train-the-Trainer - CARES Alliance Education Module - Steven Passik, PhD." August 15, 2010. MNK-T1_0001279950, at *45 (produced natively).

  Comment: As detailed in the Report at section C7, pseudo-addiction is not a reliable diagnosis; the term pseudo-addiction was developed by a physician (Haddox) who became an executive at Purdue, and a review article found that impartial scientists criticize its usage, whereas authors affiliated with the opioid sellers advocate the concept.

5. Abuse deterrent formulations prevent addiction

- "Abuse-deterrent formulations, as the name implies, make abuse of the medication more difficult." Speakers notes, Opioids in Acute Pain Management, 2014. MNK-T1_0000529044-MNK-T1_0000529126 at 9077. "Most abuse-deterrent technologies are designed to make it more difficult for medications to be abused using unintended routes of administration such as snorting or injection."

Speakers notes, Opioids in Acute Pain Management, 2014. MNK-T1_0000529044-MNK-T1_0000529126 at 9078.

Comment: The most common way that patients develop opioid problems (from dependence to misuse to addiction), is by taking them exactly as prescribed. Abuse deterrent formulations do not mitigate these problems.

Anna Lembke, M.D.

Appendix I.C: Janssen

Janssen Misleading Messaging

A. Benefits of Opioids Not Supported by Reliable Scientific Evidence

1. Opioids are effective for chronic pain

- "Effective Pain Relief Improves Physical Function In Patients With Chronic Pain. Patients with chronic low back pain receiving opioid analgesia reported significantly greater reduction in pain intensity and improved exercise performance vs patients receiving placebo." Chronic Pain Management Message Platform, August 20, 2009. JAN-MS-00068759- JAN-MS-00068828 at 8798.

  Comment: This quote is misleading because it is part of a "Chronic Pain Message Platform," but it relies on short-term studies to support claims of long-term pain relief. There are not now and have never been any reliable scientific studies showing efficacy of opioids for chronic pain. (Report at Section C4.)

2. Opioids are first-line treatment

- "Duragesic: A First-Line Choice for Chronic Around-the-Clock Opioid Therapy. Consider as first-line for patients with moderate-to-severe chronic pain who require continuous opioid analgesia: Degenerative joint disease; Chronic back pain; Cancer pain; Has been shown to be effective in certain cases of chronic neuropathic pain." Optimizing Chronic Pain Management with Duragesic, December 14, 2001. JAN-MS-00653403, at *19 (produced natively).

  Comment: By not distinguishing between cancer pain and non-malignant pain, or between acute and chronic pain, the statement is misleading, in that there was no reliable evidence that opioid therapy was effective for chronic, non-malignant pain.

3. Opioids improve function and quality of life

- "Duragesic helps patients return to activities of daily living. In a twelve-month open-label study, Duragesic significantly improved both physical and social functioning (activities such as returning to work and participating in family life). In a crossover comparison with sustained release oral morphine, patients using Duragesic had significantly better measures of social functioning, vitality, mental health and reduced pain." Information About DURAGESIC® (fentanyl transdermal system), July 16, 2002. JAN-MS-00890573-JAN-MS-00890575 at 0573.

Comment: The FDA reprimanded Janssen for its "quality of life claims, including but not limited to, 'And the #1 reason to convert your patients to the Duragesic patch: QUALITY OF LIFE,' and '...without pain, patient's sleep better, increase daily activities, and spend more quality time with their families.' Health related quality of life claims such as these require substantial supporting evidence in the form of adequate and well -controlled studies designed to specifically assess these outcomes. Therefore, without substantiation from adequate studies, the claims presented in this 'homemade' promotional piece are misleading." FDA Letter to Janssen RE: NDA 19-813, March 30, 2000. JAN-MS-00238338-JAN-MS-00238345 at 8341, see also at 8344-8345.

B. Risks Understated

1. Addiction/abuse is rare/low/uncommon/less than 1%

- "In 10 years of use, low and stable reported rate of abuse." Optimizing Chronic Pain Management with Duragesic, December 14, 2001. JAN-MS-00653403, at *17 (produced natively).

- "Iatrogenic addiction from opioid analgesia in patients experiencing pain is exquisitely rare. The Boston Collaborative Drug Surveillance Program study revealed only four cases of iatrogenic addiction among 11,882 patients without a prior history of substance abuse who received opioids for a broad range of indications." Opioidphobia PowerPoint, August 1, 2001. JAN-MS-00653426, at *25 (produced natively).

- "[P]atients may have concerns: 'I'm afraid I'll become a drug addict.' Addiction is relatively rare when patients take opioids appropriately." Duragesic Website Pages, April 10, 2006. JAN00222151, at *89 (produced natively).

- "Problematic Opioid Analgesic-Related Behavior Reported In An Evidence-Based Review Was Low. Structured evidence-based review on abuse/addiction and aberrant drug-related behaviors (ADRBs) in patients with chronic pain receiving chronic opioid analgesia. Abuse/addiction rate of 3.27% (24 studies, N = 2,507). Amongst patients with no previous or current history of abuse/addiction, the rate was 0.19%. ADRB rate was 11.5% (17 studies, N = 2,466). Among patients with no previous or current history of abuse/addiction, the rate was 0.59%." Chronic Pain Management Message Platform, August 20, 2009. JAN-MS-00068759- JAN-MS-00068828 at 8811, citing Fishbain et al. Pain Med. 2008; 9:444.

- "[S]tudies indicate that the de novo development of addiction when opioids are used for the relief of pain is low." Duragesic Information on Opioid Dependence, Tolerance and Addiction, 2002. JAN-MS-00303825, at *2 (produced natively), referencing Definitions Related to the Use of Opioids for the Treatment of Pain:

A Consensus Document from the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine.

- "Given the relatively decreased potential of misuse of long-acting (e.g., methadone) and sustained-release opioids (e.g., transdermal fentanyl) in chronic pain patients, these may be preferred over short-acting opioids." Speakers Notes, Assessing Risk of Substance Abuse, 2002. JAN-MS-00310473 at *18 (produced natively).

- Speaker's notes from a Janssen sales training presentation cite to Joranson (2000) to state that "investigators concluded that the trend of increasing medical use of opioid analgesics to treat pain does not appear to contribute to increases in the health consequences of opioid use." JAN-MS-00302787, at *29 (produced natively).

  Comment: As detailed in Section 5 of the Report, addiction is common among patients treated with opioids, and the risk of addiction increases with increasing dose and duration. The studies referenced quoting low rates of addiction, were methodologically flawed and biased by drug company sponsorship. True rates of iatrogenic addiction are probably closer to 21-29%. The Porter and Jick letter was not relevant to addiction resulting from chronic opioid therapy. The Fishbain reference did not disclose that Fishbain was an expert witness for an opioid seller (Purdue); did not disclose that Fishbain had written an earlier review that reported addiction rates as high as 18.9%; and did not disclose the numerous flaws in the Fishbain 2008 article described in Section 5 of the Main Report. The reference to Joranson did not disclose that Joranson was also a paid consultant to Purdue, and did not disclose that by 2004 even Joranson had published an updated report documenting substantially increased Emergency Department admissions for the period 1997-2002, compared to the period 1990-1996 covered by his previous article. ("In 2002, opioid analgesics accounted for 9.85% of all drug abuse, up from 5.75% in 1997." Gilson, Ryan, Joranson and Dahl, J Pain Symptom Manage. 2004 Aug; 28(2):176-88.)

2. The problem is the 'addicts,' not the drug

- "The potential for addiction is in the patient, not the opioid. Where is your patient? ~45% HIGH Long-term exposure to opioids in addicts;<1% LOW Short-term exposure to opioids in non-addict." Optimizing Chronic Pain Management with Duragesic, December 14, 2001. JAN-MS-00653403, at *66 (produced natively).

- Comment: This is an example of blaming the victim. The problem is the drug, which is as addictive as heroin. No patient is immune to addiction to prescription opioids. (Report at section C5).

3. No dose is too high

- "Doctor, there is no established ceiling dose for Nucynta ER" and "Note to Sales Representatives: A ceiling dose is the threshold at which additional dose increases produce no change in efficacy and often lead to greater side effects. It is a plateau effect that is common to most medications. However, it is important to note that pure opioid agonists, such as morphine, do not have a ceiling dose." Nucynta ER Frequently Asked Questions, November 17, 2011. JAN-MS-00016372-JAN-MS-00016397 at 6379.

- "In your practice you may titrate your patients at your discretion, based on your assessment of their pain management needs." Nucynta ER Frequently Asked Questions, November 17, 2011. JAN-MS-00016372-JAN-MS-00016397 at 6380. "There is no ceiling dose for opioids. Titrate the dose upward to obtain maximum pain relief without unacceptable side effects. Always prescribe rescue medication for breakthrough pain." Optimizing Chronic Pain Management with Duragesic, December 14, 2001. JAN-MS-00653403, at *26 (produced natively).

  Comment: The statements above are misleading because they omit that increased dose increases risk of dependence, addiction, and numerous adverse effects, including death.

4. Dependence is not a significant problem and is easily reversible

- "Opioids can be discontinued in dependent patients without withdrawal difficulties by simply tapering them over about a week." Opioidphobia PowerPoint, August 1, 2001. JAN-MS-00653426, at *24 (produced natively).

- "Physical dependence may be managed by gradually reducing the dose of the medication if the patient's physician decides it is appropriate to discontinue therapy." Duragesic Information on Opioid Dependence, Tolerance and Addiction, 2002. JAN-MS-00303825, at *1 (produced natively), (citing Passik SD, Portenoy RK, Ricketts PL. Substance abuse issues in cancer patients: part 1: prevalence and diagnosis. Oncology. 1998: 4:517-521).

  Comment: Dependence and tolerance are serious physical conditions in themselves, leading to increased doses and addiction in a subset of patients, and to long, slow, and often failed attempts at tapering. "Tapering them over about a week" would cause extreme suffering in the majority of patients on chronic opioid therapy, and may even lead some to experience suicidal thoughts and/or turn to illicit sources of opioids.

5. Tolerance - respond with higher dose

- "Tolerance does not mean that the medication has lost its effectiveness. Rather, the dose must be adjusted to achieve an effective level of pain relief." Duragesic Information on Opioid Dependence, Tolerance and Addiction, 2002. JAN-MS-00303825, at *2 (produced natively).

- "Increases in opioid doses may be required over the first few days or weeks of therapy during titration to response. Tolerance to opioid analgesia typically does not occur once an effective dose of opioid is identified and administered regularly." Opioidphobia PowerPoint, August 1, 2001. JAN-MS-00653426, at *26 (produced natively).

- "Tolerance rarely 'drives' dose escalation. Tolerance does not cause addiction." Assessing the Risk For Substance Abuse, 2002. JAN-MS-00310473, at *8 (produced natively).

  Comments: These statements are misleading, because tolerance is common, is associated with addiction, and is in fact one of the DSM-5 criteria for addiction.

6. Pseudo-addiction – respond with more opioids

- "Pseudoaddiction is a term used to describe patient behavior that can occur when pain is under-treated. Patients with unrelieved pain may become focused on obtaining medications and may seem to inappropriately seek drugs." Duragesic Information on Opioid Dependence, Tolerance and Addiction, 2002. JAN-MS-00303825, at *2 (produced natively), (citing Savage S, et al.)

- "Pseudoaddictive behaviors mimic those of true addiction, but in reality may reflect undertreatment. This may include drug-seeking behavior, taking larger than prescribed doses, and running out of medications prematurely, tolerance, and withdrawal. Although adequate pain relief should eliminate the abnormal behavior if it is truly pseudoaddictive, it is important to recognize that pseudoaddiction and addiction can coexist." Speaker's Notes, Assessing the Risk For Substance Abuse, 2002. JAN-MS-00310473, at *1(produced natively) (citing Passik et al 2000, p 73; Portenoy et al 1997, p 563.)

- "Pseudoaddiction: Syndrome of abnormal behavior resulting from undertreatment of pain that is misidentified by the clinician as inappropriate drug-seeking behavior. Behavior ceases when adequate pain relief is provided. Not a diagnosis; rather, a description of the clinical intention." Addressing the Barriers to Effective Pain Management and Issues of Opioid Misuse and Abuse, 2013. JAN-MS-01509021, at *19 (produced natively).

Comment: As detailed in the Report at Section C7, pseudo-addiction is not a reliable diagnosis; the term pseudo-addiction was developed by a physician (Haddox) who became an executive at Purdue, and a review article found that impartial scientists criticize its usage, whereas authors affiliated with the opioid sellers advocate the concept.

Anna Lembke, M.D.

Appendix I.D: Endo Pharmaceuticals

Endo Misleading Messaging

A. Benefits of Opioids Not Supported by Reliable Scientific Evidence

1. Opioids are effective for chronic pain

- "[P]ain leaders recognize the need… to arrive at a unified agenda and establish a framework that supports better understanding of this therapy and the benefits and risks of prescribing opioid medication. While the pain community must call attention to the epidemic of **chronic pain**, its undertreatment, and the **utility of opioid therapy** as a **safe and effective** strategy to relieve pain and improve functioning in appropriately selected and monitored patients, it also must acknowledge the societal and public health concerns raised by reports of increasing prescription drug abuse." "Provider Prescribing Patterns and Perceptions: Identifying Solutions to Build Consensus on Opioid Use in Pain Management—A Roundtable Discussion," American Pain Foundation. Published April 2008. (Emphasis added). At page 2 of 16, the Report states that it was "supported by an educational grant from Endo Pharmaceuticals." ENDO-OPIOID_MDL-02212377- ENDO-OPIOID_MDL-02212392 at 2380-2381.

- "Pain affects more Americans than diabetes, heart disease and cancer combined. Now is the time to build consensus on pain management **on opioid use** in America and drive perceptions towards a more balanced view. Alleviating pain in patients with legitimate medical needs remains an important medical imperative. Patients deserve optimal pain relief, which includes access to **safe and effective** pain medications balanced with appropriate risk management. When properly prescribed by a healthcare professional and taken as directed, these medications provide **important pain relief and can improve functioning**." Id. at 2381(Emphasis added)

- "A key challenge is the **lack of scientific studies that have evaluated long-term safety and efficacy** of opioids for non-cancer pain." Id. at 2380 (emphasis added).

- "The **absence of controlled clinical trials evidence must not be misinterpreted to be 'lack of evidence.'** As defined by the principles of evidence-based medicine, the cumulative experience of myriad practitioners and their patients presents a robust body of evidence; however, the need for better science in this area is abundantly clear." Id. at 2387 (emphasis added).

Comment: These quotes exemplify the Industry's misleading promotional messages, which perpetuated the unsupported claim that opioids are 'safe and effective' for 'chronic pain,' and minimized the importance of controlled trials showing safety and efficacy beyond 16 weeks. As to the claim of efficacy of opioids for chronic pain, there was not then, and there has never been, reliable evidence to support the claim. (Report at section C4.) The Endo-sponsored report tries to have it both ways. While acknowledging the lack of "scientific studies that have evaluated long-term safety and efficacy," the Report asserts that "cumulative experience" constitutes "robust evidence" under principles of evidence-based medicine. That is not correct. "Cumulative experience" is anecdotal and does not qualify as evidence-based medicine. While experience may *complement* scientific studies, experience is not a *substitute* for such studies, especially in the face of mounting evidence of harms. Further, a gold standard one-year randomized clinical trial (Krebs, 2018) demonstrated that opioids are not superior to non-opioid therapy for patients with chronic pain. This result refutes 20 years of the Industry's reliance on anecdotal, non-scientific studies to claim that long-term opioid therapy is "safe and effective."

Comment: The American Pain Foundation (AFP), which published the 2008 Report, dissolved in 2012 due to irreparable economic circumstances after a ProPublica/Washington Post article "detailed its close ties to drugmakers." The article found that APF's "guides for patients, journalists and policymakers had played down the risks associated with opioid painkillers while exaggerating the benefits." https://www.propublica.org/article/senate-panel-investigates-drug-company-ties-to-pain-groups.

2. Opioids are effective for long-term use based on short-term studies

- "Opana ER's 12 hour dosing has been proven in many patient types including opioid-naïve patients with low back pain. In a clinical trial with opioid-naïve patients, 81% of patients on OPANA ER had a >= 30% pain score reduction compared with only 52% of patients on placebo. Even more impressive, greater than 70% of these patients achieved a >= 50% pain score reduction." Endo OPANA ER Call Plan Document Message and Support Materials, February 2007. ENDO-CHI_LIT-00210473-ENDO-CHI_LIT-00210476 at 0475.

Comment: As described in Section 10.a.1 of the Report, this quote, created for its sales representatives, was a reference to an article by Katz et al which was biased and misleading, and included Endo employees as authors and was Endo sponsored. The claim that over 70% of patients on oxymorphone extended release (Opana ER) achieved greater than 50% pain relief was misleading because the ">70%" figure, who purportedly achieved > 50% pain reduction, was based on only the fraction of patients randomized to Opana who were able to complete the randomized controlled trial. In reality, 325 patients were recruited for the open

label "enriched enrollment" phase which exposed all 325 to Opana. 120 discontinued before the randomized controlled trial (RCT) even began. So only 63% (205/325) could tolerate Opana at all, let alone achieve >50% pain relief. Furthermore, following the initial enriched enrollment phase, another 33% of the subjects randomized to Opana also failed to complete the trial due to adverse effects or lack of efficacy. By ignoring the substantial percentage of patients who could not tolerate Opana at all (37%), and those who subsequently dropped out of the drug arm of the trial (33%), Endo trained its sales team to mislead physicians about its efficacy by making the false claim that "over 70%" achieved over 50% pain relief. Further, although the Katz article did not explicitly state that Opana can be used long-term for chronic pain, the training does not instruct the salesforce to limit use to 12 weeks. (ENDO-CHI_LIT-00210473-ENDO-CHI_LIT-00210476 at 0474) Also note that the Hale study, to be used for the same sales calls, explicitly stated in the abstract that Opana provides "long-term analgesia," despite a study length of only 12 weeks. The claim of "long-term analgesia" is misleading in the context of a 12-week study.

3. Opioids are first-line treatment

- Listed under benefits of Opana ER - "Proven first line therapy for opioid-naïve patients." Endo OPANA ER Call Plan Document Message and Support Materials, February 2007. ENDO-CHI_LIT-00210473-ENDO-CHI_LIT-00210476 at 0475.

  Comment: By not distinguishing between acute pain and chronic pain, this quote sends the misleading message that using Opana ER for chronic pain is evidence-based. While there is reliable evidence of efficacy of opioids for acute pain, as noted above and in the Report, there is no reliable evidence of efficacy for chronic, non-cancer pain.

B. Risks Understated

1. Opioid Therapy is "Safe"

- Comment as to the assertion in the 2008 APF Report that opioid therapy is "safe" in "appropriately selected and monitored patients,"(see above): There were numerous studies that had reported a range of addiction as high as 24% before the opioid sellers began the aggressive marketing campaign that omitted any reference to those data, and numerous additional, subsequent studies consistent with the earlier results. (Report at section C5.) There was no reliable basis to assert that addictive drugs were not addictive simply because they had been prescribed by a doctor. As noted in the Volkow/McClellan article cited in the Report, "no patient is immune from addiction." (See Report at section C1(g) n.16.) Regarding "appropriately selected and monitored patients," as detailed in the Report, we do not have any reliable tools or screening instruments to predict who will get addicted to opioids prescribed in the course of medical treatment.

2. Opioid dependence is not a significant problem and no different from other drugs

- "Physical dependence and tolerance are related phenomena that occur with chronic use of many types of drugs, including many that are not associated with addiction or abuse (such as beta blockers for high blood pressure). Both result from changes in the body as it adapts to the constant presence of the drug. Physical dependence is due to adaptive changes that cause the body to depend on the drug's actions to drive a process." Oxymorphone Learning System, Module 3, Oxymorphone Risk Management Program (For Sales Training Background Purpose Only), 2006. ENDO-CHI_LIT-00053284 - ENDO-CHI_LIT-00053335 at 3299.

  Comment: This statement is misleading because withdrawal from "beta blockers for high blood pressure" cannot compare to withdrawal from opioids, which is so painful that it can lead to suicide, death due to autonomic instability, and pursuit of illicit sources of opioids.

4. Pseudo-addiction – respond with more opioids

- The Learning System manual noted that "[t]he physician can differentiate addiction from pseudoaddiction by speaking to the patient about his/her pain and increasing the patient's opioid dose to increase pain relief." *Id.* at 3299.

- "Pseudoaddictive behaviors such as clock watching (counting down the time until the next dose) will resolve when the pain is properly treated." *Id.* at 3299.

- "The syndrome of drug-seeking behaviors that arises when a patient cannot obtain adequate relief with the prescribed dose of analgesic and seeks alternate sources or increased doses of analgesic is referred to as pseudoaddiction. This may be the result of increasing pain due to disease progression, development of a new condition, or inadequate instruction or dose provision by the clinician." Opioid Analgesics for Pain Management: Critical Thinking to Balance Benefits & Risk [Endo had financial relationships with 5/5 faculty for this CME] June 2007, expires June 2009. CHI_001222272-CHI_001222287 at 2279.

- Comment: As detailed in the Main Report (Section 7), pseudo-addiction is not a reliable diagnosis; the term pseudo-addiction was developed by a physician (Haddox) who became an executive at Purdue, and a review article found that impartial scientists criticize its usage, whereas authors affiliated with the opioid sellers advocate the concept. "Speaking to the patient" is particularly misleading advice, since numerous studies have documented the false statements provided by patients to their doctors in order to maintain access to addictive opioids.

5. Abuse Deterrent Formulations decrease risk of addiction

- "Options...1. The next generation of Opana ER was formulated using the INTAC™ technology which is designed to discourage misuse and abuse of the medication. 2. The next generation Opana ER was formulated to reduce the likelihood of abuse and misuse. 3. The FDA-approved formulation of Opana ER was developed with tamper-resistant properties to discourage abuse and misuse. 4. With a formulation that is designed to be crush-resistant, Opana ER represents the next generation of pain management medications. 5. The reformulated tablet is designed to make it more difficult for Opana ER to be split, chewed, crushed, or dissolved to release the medication more rapidly than intended." Draft Communication Messages for Opana ER, November 17, 2011. END00099670-END00099671 at 9670-9671.

- "A study of prescription opioid abusers in a drug rehabilitation program found that 80% tampered with opioid tablets to accelerate drug release by chewing or administering the drug intra-nasally or intravenously. The authors suggest that formulations that incorporate physical or pharmacologic impediments to altering the recommended routes of administration may deter tampering; The attractiveness of an opioid for abuse is in large part dependent on characteristics of the tablet formulation particularly the ease with which it can be crushed or dissolved in fluids." Letter requesting support from Julie Suko Regarding: Reformulated Opana ER (oxymorphone hydrochloride) Extended-Release Tablets, CII with INTAC® technology (Designed to be crush resistant), November 6, 2012. ENDO-OR-CID-00772464-ENDO-OR-CID-00772465 at 2464.

  Comment: Opana ER was at the center of the injection opioid epidemic in Scotts County, Indiana in 2015, that led to the spread of HIV in that community. “From November 18, 2014 to November 1, 2015, HIV infection was diagnosed in 181 case patients. Most of these patients (87.8%) reported having injected the extended-release formulation of the prescription opioid oxymorphone…Persons who reported injecting oxymorphone frequently described crushing, dissolving and cooking extended-release oxymorphone (Opana ER, Endo Pharmaceuticals).” See Peters, et.al., “HIV Infection Linked to Injection Use of Oxymorphone in Indiana, 2014-2015” N Engl J Med 2016;375:229-39, at 229 and 232. In other words, “abuse via injection” was not more difficult. The most common way that people misuse and get addicted to prescription opioids, is to ingest oral formulations orally as prescribed. Although tamper-resistant formulations may make it more difficult to crush, snort, or inject these substances, that is no protection against getting addicted to them in the first place, taken as prescribed. Further, as with Opana ER, which was supposed to be tamper resistant, addicted persons were able to crush and inject it.

Anna Lembke, M.D.

Appendix I.E: Allergan

Allergan Misleading Messaging

A. Benefits of Opioids Not Supported by Reliable Scientific Evidence

1. Opioids are effective for chronic pain

- "Longer-acting agents are more effective than short-acting agents for chronic pain; "around-the-clock" dosing for "around-the-clock pain". Managing Chronic Pain and the Importance of Customizing Opioid Treatment, October 27, 2009. ALLERGAN_MDL_01741588-ALLERGAN_MDL_01741639 at 1596.

  Comment: This quote exemplifies the claim that opioids are effective for chronic pain, which was not then, and has never been, supported by reliable evidence. (Report at section C4.)

2. Opioids are first-line treatment

- "How does Kadian fit into your prescribing habits? If first line…Thank the HCP for their business and remind them of the key features and benefits of Kadian. If not first line: Why don't you use Kadian first line?" Kadian Marketing Overview - Sales Representative Training, October 2011. ALLERGAN_MDL_00007268-ALLERGAN_MDL_00007312 at 7294. Same presentation used in February 2013, see ALLERGAN_MDL_00026506-ALLERGAN_MDL_00026552 at 6533.

  Comment: The quote above does not distinguish between acute pain and chronic pain. The implied "key feature" of Kadian is its longer duration of action for "around the clock" pain, i.e. chronic pain. While there was reliable evidence of efficacy of opioids for acute pain, as noted above and in the Report, there was no reliable evidence of efficacy for chronic, non-cancer pain. It was misleading to make a blanket statement of efficacy without making this distinction clear.

3. Opioids are safer than the alternatives

- "Maintenance therapy with opioids can be safer than the long-term use of other analgesics, such as COX-2 inhibitors, nonselective NSAIDs, or acetaminophen..." Managing Chronic Pain and the Importance of Customizing Opioid Treatment, October 27, 2009. ALLERGAN_MDL_01741588-ALLERGAN_MDL_01741639 at 1598.

- Comment: There was no reliable evidence to claim that opioids were "safer, or "perhaps" safer than NSAIDs or acetaminophen. As to NSAIDs, the best available evidence shows that opioids confer greater risk of mortality and adverse

events. (*See* Solomon study in the Report at section C4, p.66 n277.); also, the Krebs study (SPACE trial) in the Report at section C4, p.31 n108, found more adverse events in the opioid group than among the non-opioid group that consisted of acetaminophen and NSAIDs, with a small percentage of patients on tramadol.

4. Opioids improve function/quality of life

- "Proven efficacy and improvement in quality-of-life (QOL) sleep scores in patients with chronic back pain." Managing Chronic Pain and the Importance of Customizing Opioid Treatment, October 27, 2009. ALLERGAN_MDL_01741588-ALLERGAN_MDL_01741639 at 1632.

- "...Many Americans suffer from chronic or ongoing pain. It can cause you to miss work and can even keep you from enjoying life. If left untreated, pain can place stress on your body and your mental health" and "Chronic pain...can be inconvenient and can keep you from your daily tasks." The FDA objected to these statements in prior brochures. Letter to FDA from Activis, July 16, 2010. ALLERGAN_MDL_01237743-ALLERGAN_MDL_01237762 at 7750.

  Comment: The above quotes imply that opioids will improve function and mental health, when the data show little or no improvement in function with opioid therapy, and more adverse medical events. Indeed the high drop outs rates in many opioid studies, even short term, suggest that many people do not tolerate opioids. Also, studies have linked the use of opioids with depression and suicidality, not improvements in mental health. Burgeoning evidence shows significant morbidity and mortality with opioids, increasing with dose and duration.

B. Risks Understated

1. Addiction is rare

- "Opioids can be used with minimal risk in chronic pain patients without a history of abuse or addiction." Managing Chronic Pain and the Importance of Customizing Opioid Treatment, October 27, 2009. ALLERGAN_MDL_01741588-ALLERGAN_MDL_01741639 at 1596.

- Comment: Opioids cannot be used for chronic pain without imposing significant risks of addiction, dependence, withdrawal and multiple adverse effects. It is misleading to claim that risks were "minimal."

2. The problem is the 'addicts,' not the drug

- "However, despite the continued unscientific beliefs of some clinicians, there is no evidence that simply taking opioids for a period of time will cause substance

abuse or addiction. It appears likely that most substance-abusing patients in pain management practices had an abuse problem before entering practice." Kadian Learning System. ALLERGAN_MDL_01052119 – ALLERGAN_MDL_01052465 at 2254.

- Comment: This quote perpetuates the misleading idea that the problem is the addicted patient, not the inherently addictive nature of the opioid. In fact persons with no personal or family history of addiction can become dependent on, addicted to, and die from opioids through a medical prescription.

3. Tolerance - Respond with higher dose

- "Upward titration of pure opioid agonists can theoretically be continued indefinitely, because there is no absolute ceiling effect to these medications. In practice, however, although this is sometimes performed in cases of cancer pain, most physicians will try an alternative medication once they have exceeded their own comfort level with a given drug." Kadian Learning System. ALLERGAN_MDL_01052119 – ALLERGAN_MDL_01052465 at 2221.

- "Pseudotolerance—Pseudotolerance is the need for an increase in dosage that is not due to tolerance, but is due to other factors, such as disease progression, new disease, increased physic al activity, lack of compliance, change in medication, drug interaction, addiction, and deviant behavior." Kadian Learning System. ALLERGAN_MDL_01052119 – ALLERGAN_MDL_01052465 at 2305.

  Comment: The statements above are misleading because they omit that increased dose increases risk of dependence, addiction, and numerous adverse effects, including death. "Pseudotolerance" is not a recognized diagnosis, whereas "tolerance" is almost universally the reason why opioid users seek increased dosage of the drugs.

4. Pseudo-addiction – respond with more opioids

- "The problem is even more complex because some patients who are undertreated for their physical pain show the symptoms of "pseudoaddiction." Pseudoaddiction is a set of behaviors...that are exhibited by patients with inadequately treated pain, including patients with cancer pain. Pseudoaddictive behaviors are not signs of substance abuse, but rather should be considered symptoms of inadequate treatment." Kadian Learning System. ALLERGAN_MDL_01052119 – ALLERGAN_MDL_01052465 at 2150.

- "Pseudoaddiction—Pseudoaddiction is drug-seeking behavior that seems similar to addiction but is due to unrelieved pain. This behavior stops once the pain is relieved, often through an increase in opioid dose." Kadian Learning System. ALLERGAN_MDL_01052119 – ALLERGAN_MDL_01052465 at 2305.

Comment: As detailed in the Report at Section C7, pseudo-addiction is not a reliable diagnosis; the term pseudo-addiction was developed by a physician (Haddox) who became an executive at Purdue, and a review article found that impartial scientists criticize its usage, whereas authors affiliated with the opioid sellers advocate the concept.

5. Opioid dependence is easily reversible

Comment: Dependence and tolerance are serious physical conditions in themselves, leading to increased doses and addiction in a subset of patients, and to long, slow, and often failed attempts at tapering. The rate of reduction described above, "10% dose reduction per week to more rapid 25% to 50% reduction every few days," would cause extreme suffering in the majority of patients on chronic opioid therapy, and may even lead some to experience suicidal thoughts and/or turn to illicit sources of opioids.

Anna Lembke, M.D. Report

APPENDIX II

Summary of Documents from the University of Wisconsin

Pain and Policy Study Group (PPSG)

Anna Lembke, MD

APPENDIX II: Documents from the University of Wisconsin Pain and Policy Study Group

1. Documents produced by the University of Wisconsin Pain and Policy Studies Group (PPSG) in this case are supportive of Dr. Joel Saper's statements concerning the relationship between "narcopharma," as he referred to the Industry, and David Joranson, who was Director of the PPSG. (*See* Report at section C4.) These documents provide evidence that the Industry funded PPSG over a period of many years, and that PPSG, in turn, carried out programs that benefitted the Industry by increasing access to opioids and limiting regulatory scrutiny of prescribing doctors.

2. On September 9, 1996, John Stewart wrote an email to Robert Kaiko of Purdue Pharma, recounting a discussion with David Joranson and Sophie Colleau at a pain conference in Vancouver, and Dr. Colleau's follow-up letter that included a reference to a UN report concluding that "the medical need for opioids is far from being met, and recommend[ing] specific steps that should be taken by governments, non-governmental organizations and health professionals- to increase the availability and use of opioids." Stewart informs Kaiko that "In the past, we have provided modest financial support for the Wisconsin Pain Research Group (in the form of annual corporate membership) and would be inclined to provide same ($1,000 to $2,000) toward this activity." Kaiko wrote back "They are seeking support that will not only cover this, but also, subsequent issues of the publication. To date I believe they are planning for 5k from Janssen and from Purdue 4k (2k in basic support and 2k for ?# copies in Spanish for our use in Latin America.)" PPLPC013000017513.

3. On December 20, 1996, PPSG Director Joranson and several others wrote a letter to "Dear Colleague," to inform about "the new Pain & Policy Studies Group (PPSG)," following the departure of the former head of the Pain Research Group to a new position. The letter advised that, "In the US, our group will continue its work to identify and address regulatory barriers to pain management…. We will expand our work with cancer and palliative care organizations and governments in a number of countries in order to achieve more balanced opioid regulation and improved availability of opioid analgesics." PDD1701481531. The stated goals of PPSG thus included making opioids more available for treatment of pain, an objective that matched well to those of the sellers of such drugs.

4. On October 5, 2000, Director Joranson sent an email to David Haddox and Robert Kaiko of Purdue Pharma, enclosing four items that Joranson had been working on, including a document titled, "Evaluating federal and state policy for balance," which had also been sent to Dr. Sackler. Dr. Joranson's email closed with, "Hope to have a cocktail or something with you in not too long!" Haddox replied, "I think it is an excellent work product." WIS_PPSG_001791. As noted throughout the PPSG documents, the principle of "balance" asserts that efforts to control diversion and abuse should not interfere with access to prescription opioids for pain; this principle was central to the Pharmaceutical Opioid Industry's ability to achieve widespread opioid use.

5. On August 30, 2001, Joranson wrote to Chris Neumann, Senior Director of Medical Education at Purdue Pharma, to acknowledge receipt of a $75,000 grant to "help us maintain our program and accomplish our pain and policy goals." WIS_PPSG_013938.

6. On September 9, 2002, Joranson wrote to Robert Kaiko of Purdue, regarding "the points I would make about the value of our work: … 2. "We have improved state medical board policies: … Many states now have improved pain/opioid policies that address concerns about regulatory scrutiny; we developed much of it from behind the scenes, we wrote the two models that states have used, the medical board guidelines from CA and the model guidelines of the federation of state medical boards… 4. Evaluation of state policies for impediments to the use of opioids for pain." WIS_PPSG_006938

7. On October 9, 2002, Joranson again wrote to Mr. Kaiko, expressing appreciation for support provided by Purdue "for the past several years. Without your support, some of the progress reported below would not have been possible." Joranson then asked for an additional grant of $175,000 for this year, renewable for two more years. WIS_PPSG_006457.

8. On February 21, 2005, PPSG Director Joranson/PPSG gave a presentation to the American Pain Society, entitled, "Pain Policy in the U.S.: Are We Moving Forward?" The presentation included slides providing results of 3 national surveys of medical board members, in 1991, 1997, and 2004, under the heading "Education and research with medical regulators." The next slide stated that "Prescribing an opioid analgesic for more than several months to treat a patient with Chronic non-cancer pain was "Lawful/generally accepted medical practice for 12% (1991), 33% (1997) and 67% (2004) of surveyed medical boards. WIS_PPSG_000703, produced natively at *6. PPSG's Industry-funded efforts to remove prescribing restrictions significantly contributed to this drastic change in the acceptability of opioid treatment of chronic non-cancer pain.

9. Joranson's 2005 presentation continued with a description of PPSG's Model Policy Development, in particular, the FSMB Model Guidelines (1998) and FSMB Model Policy (2004), adopted in full by 13 states and in part by 12 states. The Model Policy advanced by PPSG "Recognizes need for opioids;" "Pain relief part of quality medical practice;" "Should not fear investigation:" and that "Inappropriate tx [treatment] includes over, under, non-treatment, continued ineffective tx." (Id. at *8-*10). The designation of "undertreatment" of pain as "inappropriate" was a common theme in the promotion of opioids as the solution. The question of undertreatment of pain and the scope of the population arguably affected vary widely according to how the terms are defined. Regardless, the use of long-term opioid therapy is not and has never been the solution to chronic non-cancer pain.

10. Joranson' presentation included a slide on "The Principle of Balance," which stated, "Central to protecting public health and safety: Opioids are safe and effective, necessary," and that "Opioids have potential for abuse, pose risks." (Id. at *16). Reliable scientific evidence demonstrates that opioids are dangerous and deadly, not "safe;" no reliable scientific evidence demonstrated that opioids were effective for the treatment of chronic non-cancer pain. Joranson's industry-funded presentation was misleading.

11. Another of Joranson's February 2005 presentation slides listed "16 States Improved Pain Policies (2000-2003), including Ohio among them. "Examples of Policy Changes" included "Encourage pain management, pain management part of quality professional practice, address fear of regulatory scrutiny." (Id. at *18-*19). Eight slides are devoted to the topics of diversion and abuse (Id. at 23*-*30). The presentation stated, "The reasons for increased abuse should be studied, taking into consideration all the sources of abused opioids, including deliberate criminal activities to divert opioids from all levels of the distribution system. Source and amount matter. Meanwhile, we should ensure that efforts to address abuse and diversion do not interfere in pain management." (Id. at *31). No slides in the presentation are devoted to risk of addiction or the powerful addictive properties of prescription opioids, including the risk to individuals who are receiving opioids as medical treatment, and not only to "abusers."

12. On June 6, 2005, PPSG Director David Joranson and Assistant Director Aaron Gilson wrote to Robert Kaiko, VP of Clinical Research at Purdue and Pamela Bennett, Purdue, Director of Advocacy, to express appreciation for "the last three years of financial support that Purdue Pharma has provided to [PPSG], amounting to $100,000 annually for the US program and $175,000 annually for the international program." This amounts to $825,000 of financial support to PPSG from Purdue alone, in that 3-year period. The letter summarized PPSG's "recent achievements" and requested an additional $2.2 million from Purdue for the years 2006-2010. The first listed "achievement was as follows: "In the USA, between 2000 and 2003, 16 States took legislative and regulatory actions to improve their pain policies. Many of these actions were based on our evaluations, recommendations and technical assistance and were accomplished in collaboration with many governmental and nongovernmental groups which use PPSG policy evaluations as a road map." WIS_PPSG_008286.

13. In an August 2005 email thread referencing the enactment of the "North Dakota Pain Bill," an email was sent to Aaron Gilson, Assistant Director of PPSG, asking: "Did you guys have a hand in this one? This is certainly what I've espoused for years, since we realized intractable pain acts weren't really that helpful—that all we needed in statute was a statement that practitioners could legally prescribe opioids for pain." WIS_PPSG_000026; WIS_PPSG_000036. Gilson responded, "I'm impressed that you could detect our finger prints...I'll wear gloves next time. Yes, we worked with Bruce Levi, Executive Director of the North Dakota Medical Association, to change ND's IPTA[Intractable Pain Treatment Act] to a general pain statute, which also removed the prescribing restriction for 'addicts.'" WIS_PPSG_000026; WIS_PPSG_000036. This exchange is indicative of not only the type of PPSG projects that benefited the Industry by easing prescribing restrictions and penalties, but also shows the surreptitious, behind-the-scenes nature of PPSG's efforts.

14. In a November 2005 "Prospectus," PPSG listed a number of policies and programs to attract financial support. The Prospectus described PPSG's promotion of "the principle of 'balance' which recognizes that policies aimed at preventing drug abuse must not interfere with medical practice and patient care." To promote that policy, PPSG published "State Profiles that identify provisions in each state that have the potential to enhance or impede pain management. … PPSG assigns grades to each state to draw attention to the need to improve pain policy. … A Progress Report Card compared the policies in 2003 with those in 2000 and found that many states had improved the degree of balance in their pain and regulatory policies. PPSG

identifies and recommends 'best' or model policies and assists in their development." WIS_PPSG_008292 at pp. 2-3. The "Accomplishments" section of the Prospectus stated, "PPSG played a central role in revising the Federation of State Medical Board's Model Guidelines on the Use of Controlled Substances for Pain Management, now entitled Model Policy for the Use of Controlled Substances for Pain Management." (Id. at p. 4). The FSMB Model Guidelines played a significant role in exacerbating the prescription opioid epidemic, by eliminating or reducing restrictions on use of opioids for pain, and by threatening regulatory action for 'undertreated pain.'

15. PPSG also worked with the FSMB to develop and present an educational program for "workshops for state medical board members held across the U.S.; PPSG staff served as faculty, and administered a pre- and post-test survey to evaluate changes in knowledge and attitudes as a result of workshop participation." WIS_PPSG_008292, 11/30/2005.

16. On December 1, 2005, Joranson and Gilson of PPSG wrote to Bobbie Sue Brown, Clinical Development & Education Manager-Southwest, at Endo Pharmaceuticals, recounting the work of PPSG and requesting $225,000 for the period 2006-2008. WIS_PPSG_007994.

17. A document titled, "U.S. Program Accomplishments: July 2009-June 2010," stated: "PPSG remains a member of the Federation of State Medical Boards Research and Education Foundation's advisory committee that recently developed a handbook to educate physicians about the Federation's Model Policy to promote safe and effective prescribing and reduce the risk of abuse, addiction, and diversion of opioids and other controlled substances in office-based pain management; the Handbook was published mid-2007 and is being made available to state medical boards to distribute to their licensees. [Fishman SM. Responsible opioid prescribing: A physician's guide. Washington, DC: Waterford Life Sciences; 2007.]" WIS_PPSG_007680, 02/07/2011, at p. 3.

18. The 2007 Fishman Handbook encouraged use of prescription opioids for chronic pain, despite absence of reliable evidence of long-term efficacy. Dr. Fishman's disclosure for a Continuing Medical Education (CME) program based on the Handbook listed Purdue Pharma, Endo, Janssen and Cephalon among his financial supporters. https://archive.org/stream/279187-responsible-opioid-prescribing-info/279187-responsible-opioid-prescribing-info_djvu.txt. The CME website listed the consortium members who supported publication of the Handbook, including Purdue Pharma, Endo, Cephalon, Alpharma, and the PPSG; the CME target audience was described as "Physicians who prescribe opioid analgesics as part of pain management strategies in their clinical practice." (Id.) In short, PPSG cooperated with the Pharmaceutical Opioids Industry to produce a Handbook funded by the Industry to promote its views of "responsible prescribing;" that book was then used to "educate" physicians for CME credit, to be earned by reading the book and passing an online test on its contents.

19. The "U.S. Program Accomplishments: July 2009-June 2010" document also included the following entry: "PPSG published a review article describing the implications of inaccurate addiction-related terminology, contained in current federal and state laws, regulations, and guidelines/policy statements, on effective pain management and patient care; data used to inform sections of this manuscript was obtained through a recently-completed grant to examine the legislative and regulatory origins of restrictive policy language that currently is present in

state law and has a potential to interfere with the adequate and effective use of controlled substances for pain management. [Gilson AM. The concept of addiction in law and regulatory policy: A critical review. Clinical Journal of Pain. 2010; 26(1):70-77.]" WIS_PPSG_007680 (Emphasis added). Removing restrictions and interference with opioid prescribing were the stated goals of PPSG and aligned with its Industry funders.

20. A PPSG Spreadsheet lists financial contributions from the Pharmaceutical Opioid Industry between November 2000 and August 2007, as follows: Purdue Pharma, $1,256,500; Janssen/J & J: $238,990; Endo, $140,000; Ortho-McNeil, $125,000; Cephalon, $25,000; Alpharma, $25,000; Roxane, $15,000; and Abbott, $15,000 for a total of $1,840,490. The spreadsheet lists 27 separate contributions by Purdue, and 10 each by Janssen/J&J and Endo; the frequency and collegial nature of the communications between PPSG and company representatives like David Haddox suggests a cooperative relationship. Additional payments occurred outside of the years covered by the spreadsheet. WIS_PPSG_007783.

21. A presentation by Joranson on February 16, 2008 disclosed financial relationships with Abbott, Alpharma, Cephalon, Endo, Ortho-McNeil and Purdue Pharma.WIS_PPSG_007991**.** However, Joranson's presentation slides did not include such disclosures in February 2005. WIS_PPSG_000703.

22. A 2011 spreadsheet lists the following contributions as "Pending": Actavis, "to be $55k;" Allergan $50,000; Endo, $46,106; $649,779; $46,057; and $75,000; Janssen Ortho Pricara, $50,000; and $10,000; and Purdue, $50,000. WIS_PPSG_003892.

23. These documents provide supportive evidence for my opinion that one of the ways that the Pharmaceutical Opioid Industry created the opioid epidemic in the United States was by funding the PPSG to "educate" the medical community as to the "necessity" for such drugs, to influence state legislatures to increase access while loosening restrictions on prescribing, and to change the very culture of opioid prescribing, by suggesting that failing to prescribe opioids was tantamount to 'undertreating' pain and violating a patient's 'rights.'

Anna Lembke, M.D. Report

EXHIBIT A

Curriculum Vitae and List of Publications

Anna Lembke, M.D.
Stanford University School of Medicine
Department of Psychiatry and Behavioral Sciences
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Education and Training

1985-1989	Yale University (BA, Humanities; *summa cum laude*) New Haven, CT
1989-1990	University of Beijing (Mandarin Chinese) Beijing, China
1992-1995	Stanford University School of Medicine (MD) Stanford, CA
1995-1997	Residency, Pathology Stanford University School of Medicine, Stanford, CA
1997-1998	Internship, Internal Medicine Highland Hospital, Alameda, CA
1998-2000	Residency, Psychiatry Stanford University School of Medicine, Stanford, CA
2000-2002	Fellowship in Mood Disorders, Psychiatry and Behavioral Sciences Stanford University School of Medicine, Stanford, CA

Honors and Awards

1989	Yale University *Summa cum laude* in Humanities
1989	Yale University Outstanding Contributor to Community Life Award
1989	Yale University Yale-China Fellowship
1995	Stanford University School of Medicine Outstanding Teacher in Structural Biology Award
1999	Janssen Scholar Research on Severe Mental Illness Award

2000	Medical Education and Research Foundation (MERF) Travel Scholarship Award
2000	American Psychiatric Association and Lilly Psychiatric Research Award
2000	National Institute of Mental Health Research Fellowship Award
2002	American College of Psychiatrists Laughlin Fellowship Award
2009	Alcohol Medical Scholars Program Scholarship Award
2011	Association of Medical Education and Research Substance Abuse Travel Scholarship Award
2013	Stanford University School of Medicine Faculty Fellowship Award
2014	Stanford University School of Medicine Department of Psychiatry Excellence in Academic Teaching Award
2015	Stanford University School of Medicine Department of Psychiatry Chairman's Clinical Innovation Award
2017	Johns Hopkins Bayview Internal Medicine Visiting Professorship Award
2018	Vanderbilt University School of Medicine Flexner's Deans' Lecture Award
2018	University of Kansas School of Medicine Alpha Omega Alpha Visiting Professorship Award
2018	Evanston Township High School Distinguished Alumni Award
2018	Stanford University School of Medicine Department of Psychiatry Excellence in Academic Teaching Award

Academic and Clinical Appointments

Current Appointments

2012-present Chief, Addiction Medicine Dual Diagnosis Clinic
Department of Psychiatry and Behavioral Sciences
Stanford University School of Medicine, Stanford, CA

2013-present Program Director, Addiction Medicine Fellowship
Department of Psychiatry and Behavioral Sciences
Stanford University School of Medicine, Stanford, CA

2016-present Courtesy Appointment
Department of Anesthesiology and Pain Medicine
Stanford University School of Medicine, Stanford, CA

2017-present Medical Director, Addiction Medicine
Stanford Health Care and Stanford University Hospital, Stanford, CA

2017-present Associate Professor of Psychiatry and Behavioral Sciences
Stanford University School of Medicine, Stanford, CA

Prior Appointments

2010-2017 Assistant Professor
Department of Psychiatry and Behavioral Sciences
Stanford University School of Medicine, Stanford, CA

2003-2010 Instructor
Department of Psychiatry and Behavioral Sciences
Stanford University School of Medicine, Stanford, CA

Other Previous Employment

1991-1992 Bilingual Teacher (grades K-8), State Certified in Chinese (Mandarin)
Healy Elementary School, Chicago, IL

1989-1990 English Teacher, Yali Middle School
Changsha, China

Medical Licensure and Specialty Board Certification

1995 California medical license #A62241

2003 Diplomate, American Board of Psychiatry and Neurology
Certificate #51988; recertified 2/18/2013

2012	Diplomate, American Board of Addiction Medicine Certificate #2012288; certified 12/15/2012 (Exp date 12/31/2022)
2013	DEA-X waivered to prescribe buprenorphine products

Educational Leadership

2003-2005	Chair, Curriculum Committee Department of Psychiatry and Behavioral Sciences Stanford University School of Medicine
2009-present	Course Director, CME-accredited monthly Stanford seminar series for community physicians - "Closing the Gap: Moving towards Best Practices in Psychiatry"
2012-2014	Principal Organizer and Lecturer of the free Buprenorphine Certification Course and CURES registration for Stanford University
2013-present	Program Director, Addiction Medicine Fellowship Department of Psychiatry and Behavioral Sciences Stanford University School of Medicine
2014	Expert Consultant, Alcohol and Women Task Force Office of the Vice Provost for Student Affairs, Stanford University
2014-2016	Annual Medical Student Town Hall Meetings on Wellness and Professionalism (Issues of Substance Use and Addiction) Office of the Dean of the School of Medicine, Stanford University
2015-2016	Expert Consultant, Alcohol and Other Drug (AOD) Subcommittee of the Mental Health and Well-Being Advisory Committee Stanford University
2016-present	Chair, Addiction Medicine Task Force Stanford University School of Medicine (Goal: to create a new curriculum for addiction medicine and safe opioid prescribing for medical students)
2017-present	Committee on Professionalism Stanford University School of Medicine

Teaching and Mentoring

Stanford University School of Medicine Ongoing Lecture Series

2002-present Course Director, Addiction Medicine, Stanford University School of Medicine

2009-present Course Director, Stanford CME series "Closing the Gap in Psychiatry"

2012-present Course Lecturer, Substance Use Disorders, Stanford Child Psychiatry Fellowship

2012-present Course Lecturer, Substance Use Disorders, Stanford Palliative Care Fellowship

2012/'14/'16 Biennial lecture on addiction medicine to Stanford undergraduates as part of the Hum Bio Molecular and Cellular Physiology 256 seminar

Stanford University School of Medicine Clinical Supervision (weekly year round)

2002-present	Inpatient Psychiatry	Medical Students, Residents/Fellows
2010-present	Addiction Med/Dual Dx Clinic	Medical Students, Residents/Fellows
2013-present	Pain and Addiction Clinic	Addiction Medicine/Pain Fellows

Stanford University School of Medicine MedScholars Advisor

2016 MedScholar Advisor for Inbar Raber, *Qualitative Assessment of Clerkship Students' Perspectives of Pain and Addiction Curriculum at Stanford*, Stanford University School of Medicine, Stanford, California

2017 MedScholar Advisor for Alex Ball, *Developing the Addiction Curriculum at Stanford*, Stanford University School of Medicine, Stanford, California

Stanford University and Palo Alto University PsyD Consortium Dissertation Review

2016 Dissertation Advisor and Review Committee Member for Jennifer Bielenberg, PsyD Consortium, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California

2017 Dissertation Chair and Review Committee Chair for Shelby Schwartz, PsyD Consortium, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California

2018 Dissertation Chair and Review Committee Chair for Julia Yasser, PsyD Consortium, Department of Psychiatry and Behavioral Sciences, Stanford

University School of Medicine, Stanford, California

Professional Associations

2011-present Member, American Society of Addiction Medicine (ASAM)

2011-present Member, California Society of Addiction Medicine (CSAM)

2015-present Board Member, California Society of Addiction Medicine (CSAM)

2011-2016 Member, Association of Medical Education and Research in Substance Abuse (AMERSA)

2016-2018 President, Addiction Medicine Fellowship Directors Association (AMFDA)

2019-2021 Board Member, American College of Academic Addiction Medicine (ACAAM)

Regional and National Service

Professional Societies and Advisory Boards and Committees

2012-2015 Facilitator, California Society of Addiction Medicine Annual Conference, San Francisco, California

2013-present Member, Public Policy Committee, California Society of Addiction Medicine

2013-2014 Representative, American Board of Addiction Medicine Practice Improvement and Performance Measures Action Group (PIPMAG)

2013-present Representative, American Board of Addiction Medicine Fellowship Development Working Group

2013-present Board Member, Medical Education and Research Foundation (MERF) for the Treatment of Addiction

2014-present Board Member, California Society of Addiction Medicine Education Committee

2014-present Board Member, California Society of Addiction Medicine State-of-the-Art Conference Planning Group

2015-present Elected to the Board of Directors, Member at Large, California Society of Addiction Medicine

2015-2016 American Society of Addiction Medicine representative to the PCORI Workshop: *Long-Term Use of Opioids for Chronic Pain*

2015-2017 Appointed by Governor Jerry Brown to the California Research Advisory Panel, January 2015

2015-present Member, Public Policy Committee, American Society of Addiction Medicine

2015-2016 Chair of the Conference Planning Committee for the Annual Addiction Medicine Review Course, California Society of Addiction Medicine

2016-2017 Invited Board Member, Physicians for Responsible Opioid Prescribing (PROP)

2016-2017 Vice-Chair of the Planning Committee, California Society of Addiction Medicine Annual Conference

2016-2018 President, Addiction Medicine Fellowship Directors Association (AMFDA)

Editorial Work

2003-2004 Guest Editor, *Academic Psychiatry*, Issue on Women in Academia

2013-2014 Reviewer, *How to Find Quality Addiction Treatment* CASAColumbia Patient Guide

2014-2017 Associate Editor, *Addiction Science and Clinical Practice (ASCP)*

Ad-Hoc Manuscript/Report Review

Academic Psychiatry
Addiction
Addiction Science and Clinical Practice
Agency for Healthcare Research and Quality (AHRQ)
American Journal of Psychiatry
Archives of General Psychiatry
Asian Journal of Psychiatry
Biological Psychiatry
Bipolar Disorder
British Medical Journal
Culture, Medicine, and Psychiatry
Current Biomarker Findings
Expert Opinion on Pharmacotherapy

Expert Review of Neurotherapeutics
General Hospital Psychiatry
Healthcare: The Journal of Delivery Science and Innovation
Journal of Addiction Science and Clinical Practice
Journal of Affective Disorders
Journal of the American Medical Association
Journal of Psychiatric Research
Journal of Studies on Alcohol and Drugs
Medical Journal of Australia
New England Journal of Medicine
New Recovery Community Institutions
Pain Medicine
Psychological Medicine
Rationality and Society
Sociologic Forum
Substance Abuse

Current Funding

2015-2020 Funder: National Institute of Alcohol Abuse & Alcoholism
Title: CNS Deficits: Interaction of Age & Alcoholism, R01 AA005965
Role: Investigator (MPI: Pfefferbaum & Zahr)

2018-2019 Funder: Department of Governmental Relations, Stanford Hospital/Clinics
Title: Addiction Medicine Peer Mentor Program
Role: Investigator (MPI: Chesler and Gallagher)

2018-20120 Sponsor: Soberlink
Title: Using Remote Monitoring Devices in the Treatment of Alcohol Withdrawal
Role: Primary Investigator

Previous Funding

2000-2001 Funder: American Psychiatric Association and Eli Lilly Training Grant

Title: Facial Emotion Processing in Patients with Bipolar Disorder
Role: PI

2001-2002 Funder: National Institute of Mental Health Research Fellowship
Title: Facial and Vocal Emotion Processing in Mood Disorders
Role: PI

2001-2003 Funder: National Institute of Mental Health
Title: Systematic Treatment Enhancement Program for Bipolar Disorder

Role: Site-Investigator (PI: Sachs, Mass General)

2008-2010 Funder: National Institute of Mental Health
Title: HPA Axis in Psychotic Depression, 2 RO1 MH050604-12
Role: Co-Investigator (PI: Schatzberg)

2009-2014 Funder: National Institute on Drug Abuse
Title: Extended Treatment for Smoking Cessation, R01 DA017441
Role: Co-Investigator (PI: David)

2011-2014 Funder: National Institute of Health
Title: Genetics of Symptomatology and Treatment Response in Depression
Role: Investigator (PI: Murphy)

2012-2015 Funder: Michael Alan Rosen Foundation
Title: Screening and Brief Intervention for Substance Misuse/Abuse
Role: Co- PI (Co-PI: Humphreys)

2013-2014 Funder: Stanford Center at Peking University (SCPKU)
Title: Narratives of Addiction in Contemporary China
Role: PI

2014-2015 Funder: Peter F. McManus Charitable Trust, SPO #112718
Title: Exploring Physician Opioid Prescribing Using a Novel Approach to Data Mining of Medical Records
Role: PI

2014-2015 Funder: American Board of Addiction Medicine/Conrad N. Hilton Foundation
Title: 2014 Next Generation Award for Adolescent Substance Use Prevention
Role: PI

2014-2015 Funder: Stanford Center for Continuing Medical Education (SCCME)
Title: Prescription Drug Abuse – Compassionate Care for a Complex Problem
Role: PI

2015-2016 Funder: American Board of Addiction Medicine/Conrad N. Hilton Foundation
Title: 2015 Next Generation Award for Adolescent Substance Use Prevention
Role: PI

2016-2017 Funder: Stanford Center for Continuing Medical Education (SCCME)

Title: Tapering Patients off of Chronic Opioid Therapy
Role: PI

2017 Funder: VA Center for Innovation to Implementation
Title: The Hidden Role of Benzodiazepines in the Prescription Drug Epidemic
Role: Small grant awardee

Bibliography

Peer-Reviewed Original Research

1. Crowley RS, **Lembke A**, Horoupian DS. Isolated Meningeal Vasculopathy Associated with Clostridium Septicum Infection *Neurology* 1997; 48(1):265-7.

2. **Lembke A**, Ketter TA. Impaired Recognition of Facial Emotion in Mania *American Journal of Psychiatry* 2002; 159(2):302-4.

3. Menon V, Levitin DJ, Smith BK, **Lembke A**, Krasnow BD, Glazer D, Glover GH, McAdams S. Neural Correlates of Timbre Change in Harmonic Sounds *Neuroimage* 2002; 17(4):1742-54.

4. Janenawasin S, Wang PW, **Lembke A**, Schumacher M, Das B, Santosa CM, Mongkolcheep J, Ketter TA. Olanzapine in Diverse Syndromal and Subsyndromal Exacerbations of Bipolar Disorders *Bipolar Disorders* 2002; 4(5):328-34.

5. DeBattista C, **Lembke A**, Solvason HB, Ghebremichael R, Poirier J. A Prospective Trial of Modafinil as an Adjunctive Treatment of Major Depression. *Journal of Clinical Psychopharmacology* 2004; 24(1):87-90.

6. **Lembke A**, Miklowitz D, Otto M, Wisniewski S, Sachs N, Thase M, Ketter TA. Psychosocial Service Utilization by Patients with Bipolar Disorders. *Journal of Psychiatric Practice 2004*; 10(2):81-87.

7. Miklowitz, D.J., Otto, M.W., Wisniewski, S.R., Araga, M., Frank, E., Reilly-Harrington, N.A., **Lembke, A**., Sachs, G.S. Psychotherapy, Symptom Outcomes, and Role Functioning Over One Year among Patients with Bipolar Disorder. *Psychiatric Services* 2006; 57(7):959-65.

8. **Lembke, A**., Bradley, K.A., Henderson, P., Moos, R. Harris, A.H.S., Alcohol Screening Scores and the Risk of New-Onset Gastrointestinal Illness or Related Hospitalization. *Journal of General Internal Medicine*, 2011; 26(7):777-782.

9. Che, A., Gomez, R., Keller, J., **Lembke, A.,** Tennakoon, L., Cohen, G., Schatzberg, A., The relationships of positive and negative symptoms with neuropsychological functioning and their ability to predict verbal memory in psychotic major depression. *Psychiatry Research*, 2012; 198(1):34-8. *Served as study physician and contributed to*

manuscript preparation.

10. Harris, A.H.S., **Lembke, A.,** Henderson, P., Gupta, S., Moos, R., & Bradley, K.A. Risk of Future Trauma Based on Alcohol Screening Scores: A Two-Year Prospective Cohort Study Among US Veterans. *Addiction Science & Clinical Practice*, 2012; 7(1):6. *Contributed to data analysis and manuscript preparation.*

11. **Lembke, A**., Gomez, R., Tenakoon, L., Keller, J., Cohen, G., Williams, G. H., Kraemer, F.B., Schatzberg, A.F., The mineralocorticoid receptor agonist fludrocortisone, differentially inhibits pituitary-adrenal activity in humans with psychotic major depression. Psychoneuroendocrinology, 2012, 38(1):115-121.

12. Del Re, A.C., Gordon, A.K., **Lembke, A**. Harris, A.H.S., Utilization of Topiramate to Treat Alcohol Use Disorders in the Veterans Health Administration. *Addiction Science and Clinical Practice*, 2013;8(12). *Contributed to data analysis and manuscript preparation.*

13. Harris, AHS, Ellerbe, L, Reeder, RN, Bowe, T, Gordon, AJ, Hagedorn, H, Oliva, E, **Lembke, A**, Kivlahan, D, Trafton, JA. Pharmacotherapy and Alcohol Dependence: Perceived treatment barriers and action strategies among Veterans Health Administration service providers. *Psychological Services*, 2013; 10(4):410-419. *Contributed to data analysis and manuscript preparation.*

14. Kelley, R., Garrett, A., Cohen, J., Gomez, R., **Lembke, A.,** Keller, J., Reiss, A.L., Schatzberg, A. Altered brain function underlying verbal memory encoding and retrieval in psychotic major depression. *Psychiatry Research: Neuroimaging*, 2013; 38 (1):115-121. *Served as study physician and contributed to manuscript preparation.*

15. Yuen KW, Garner JP, Carson DS, Keller J, **Lembke A,** Hyde SA, Kenna HA, Tennakoon L, Schatzberg AF, Parker KJ. Plasma oxytocin concentrations are lower in depressed vs. healthy control women and are independent of cortisol. *Journal of Psychiatric Research*, 2014; 51:30-6. *Served as study physician and contributed to manuscript preparation.*

16. Schatzberg AF, Keller J, Tennakoon L, **Lembke A,** Williams G, Kraemer FB, Sarginson JE, Lazzeroni LC, Murphy GM. HPA axis genetic variation, cortisol and psychosis in major depression. *Molecular Psychiatry*, 2014; 19(2):220-7. *Served as study physician and contributed to manuscript preparation.*

17. Maclean D, Gupta S, **Lembke A**, Manning CD, Heer J. Forum77: An Analysis of an Online Health Forum Dedicated to Addiction Recovery. *ACM Computer-Supported Cooperative Work (CSCW), https://idl.cs.washington.edu/papers/forum77/;* 2015; Best Paper Honorable Mention. *Contributed to data analysis and manuscript preparation.*

18. **Lembke, A.**, Cheng, Niushen. A Qualitative Study of Treatment-Seeking Heroin

Users in Contemporary China, *Addiction Science and Clinical Practice*, 2015;10:23.

19. Chen, J., Humphreys, K., Shah, N.H., **Lembke, A.** Distribution of Opioids by Different Types of Medicare Prescribers, *JAMA Internal Medicine*, 2016; 176(2):259-261.

20. Haug, N.A., Bielenberg, J., Linder, S. H., **Lembke, A.** Assessment of provider attitudes toward #naloxone on Twitter. *Substance Abuse*, 2016; 37(1):35-41.

21. **Lembke, A.,** Chen, J. Use of Opioid Agonist Therapy for Medicare Patients in 2013. *JAMA Psychiatry*, 2016;73(9):990-992. doi:10.1001/jamapsychiatry.2016.1390

22. Keller, J., Gomez, R., Williams, G., **Lembke, A**., Lazzeroni, L., Murphy, G.M. Jr, Schatzberg, A.F. HPA Axis in Major Depression: Cortisol, Clinical Symptomatology, and Genetic Variation Predict Cognition, *Molecular Psychiatry*, Feb; 19(2): 220–227. doi: 10.1038/mp.2016.120 2016. *Served as study physician and contributed to manuscript preparation.*

23. Stein, M., Kanabar, M., Anderson, B.J., **Lembke, A**., Bailey, G.L. Reasons for Benzodiazepine Use Among Persons Seeking Opioid Detoxification, *Journal of Substance Abuse Treatment*, 2016; September; 68: 57–61. *Contributed to data analysis and manuscript preparation.*

24. Leyro, T. M., Crew, E. E., Bryson, S. W., **Lembke, A**., Bailey, S. R., Prochaska, J. J., Henriksen, L., Fortmann, S. P., Killen, J. D., Killen, D. T., Hall, S. M., David, S. P. Retrospective analysis of changing characteristics of treatment-seeking smokers: implications for further reducing smoking prevalence. *BMJ* 2016; 6 (6). *Served as study physician and contributed to manuscript preparation.*

25. Laude, J. R., Bailey, S. R., Crew, E., Varady, A., **Lembke, A.,** McFall, D.,David, S. P. (2017). Extended treatment for cigarette smoking cessation: A randomized control trial. *Addiction*. https://doi.org/10.1111/add.13806

26. Prekupec, M.P., Sussman, R.S., Sher, Y., **Lembke, A.** Relapse on ketamine followed by severe and prolonged withdrawal: A cautionary case and review of potential medical therapies. *J Nat Sci*, 3(10):e450, 2017.

27. Raber, I., Ball, A., Papac, J., Aggarwal, A., Sussman, R., Basaviah, P., Newmark, J. **Lembke, A.** Qualitative Assessment of Clerkship Students' Perspectives of the Topics of Pain and Addiction in their Preclinical Curriculum, *Academic Psychiatry*, 2018;42:664, doi: 10.1007/s40596-018-0927-1

28. Raheemullah, A., **Lembke, A.** Initiating Opioid Agonist Treatment for Opioid Use Disorder in the Inpatient Setting: A Teachable Moment, *JAMA Internal Medicine*, 2019

Peer Reviewed Perspectives and Reviews

29. **Lembke A**. A Piece of My Mind: "A letter from the foreign legion" *JAMA*, 1996; 276(21):1704.

30. Barry JJ, Huynh N, **Lembke A**. Depression in Individuals with Epilepsy *Current Treatment Options in Neurology*, 2000; 2(6):571-585.

31. **Lembke A**. "Mind" and "Brain" *American Journal of Psychiatry*, 2001; 158(11):1939-1940.

32. DeBattista C, Trivedi M, Kern J, **Lembke A**. The Status of Evidence-Based Guidelines and Algorithms in the Treatment of Depression *Psychiatric Annals*, 2002; 32(11):658-663.

33. Sommer B, Fenn H, P. P, DeBattista C, **Lembke A**, Wang P, Flores B. Safety of Antidepressants in the Elderly. *Expert Opinion on Drug Safety*, 2003; 2(4):367-383.

34. **Lembke A**. A Friday in the Life of an Academic Psychiatrist *Academic Psychiatry*, 2003; 27(3):214-215.

35. Barry J.J., **Lembke A.**, Bullock K.D.. Current Status of the Utilization of Antiepileptic Treatments in Mood, Anxiety and Aggression: Drugs and devices. *Clinical EEG and Neuroscience*, 2004; 35(1):4-13. *Contributed to manuscript preparation.*

36. **Lembke, A**. Why is this Special Issue on Women's Professional Development in Psychiatry Necessary? *Academic Psychiatry*, 2004 28(4):275-277.

37. Debattista, C**., Lembke, A.,** Update on Augmentation of Antidepressant Response in Resistant Depression. *Current Psychiatry Report*, 2005; 7(6):435-40.

38. **Lembke A**, Johnson K, DeBattista C. Depression and Smoking Cessation: Does the Evidence Support Psychiatric Practice? *Neuropsychiatric Disease and Treatment*, 2007; 3(4):1-7.

39. DeBattista, C, **Lembke, A**. Psychotic Major Depression: Phenomenology and the Pursuit of Optimal Treatment. *Primary Psychiatry*, 2008; 15(4):59-64.

40. Schatzberg, A.F., Solvason, H.B., Keller, J., **Lembke, A.** Antidepressant Interventions in the HPA system. *Journal of Affective Disorders*, 2008; 107(Suppl.1):S40-S41.

41. **Lembke, A**. Depressed Smokers: A Guide to Treatment Based on the Evidence. *Depression: Mind and Body*, 2009;4(3):96-101.

42. **Lembke, A**. Optimal Dosing of Lithium, Valproic Acid, and Lamotrigine in the Treatment of Mood Disorders. *Primary Psychiatry*, 2009; 16(10):33-38.

43. **Lembke, A**., Humphreys, K., Moderation Management: A Mutual-Help Organization for Problem Drinkers who are not Alcohol Dependent. *Journal of Groups in Addiction and Recovery*, 2012; 7(2-4):130-141.

44. **Lembke, A**. Time to Abandon the Self-Medication Hypothesis in Patients with Psychiatric Disorders. *The American Journal of Drug and Alcohol Abuse*, 2012, 38(6):524-529.

45. **Lembke, A**. Why doctors prescribe opioids to known opioid abusers. *New England Journal of Medicine*. October 25, 2012; 367(17):1580-1581

46. **Lembke, A.** From Self-Medication to Intoxication: Time for a Paradigm Shift. *Addiction*, 2013; 108(4):670-671.

47. Humphreys, K., **Lembke, A.** Recovery oriented policies and care systems in the U.K. and the USA. *Drug and Alcohol Review*, 2014; 33 (1):13-18.

48. **Lembke, A**, Humphreys, K. A Call to Include People with Mental Illness and Substance Use Disorders Alongside 'Regular' Smokers in Smoking Cessation Research, *Tobacco Control*, 2015;25(3):261-2.

49. **Lembke, A.,** Humphreys, K., Newmark, J. Weighing the Risks and Benefits of Chronic Opioid Therapy, *American Family Physician*, 2016; 93(12):982-990.

50. Ogbonna, C., **Lembke, A.** Tapering Patients Off of Benzodiazepines, *American Family Physician*, 2017 Nov 1;96(9):606-608.

51. **Lembke, A**. The Opioid Epidemic is a Symptom of our Faltering Health Care System, *The British Medical Journal*, published online October 30, 2017 http://blogs.bmj.com/bmj/2017/10/31/anna-lembke-the-opioid-epidemic-is-a-symptom-of-our-faltering-healthcare-system/

52. **Lembke, A.** Why Addiction Should Be Considered a Disease, *Judges' Journal*, 2018 Jan; Volume: 57 Issue: 1

53. **Lembke, A.** Ottestad, E., Schmiesing, C. Patients Maintained on Buprenorphine for Opioid Use Disorder Should Continue Buprenorphine Through the Perioperative Period, *Pain Medicine*, 2018 https://doi.org/10.1093/pm/pny019

54. **Lembke, A.,** Papac, J., Humphreys, K. Our Other Prescription Drug Problem, *NEJM*, Feb 22, 2018.

55. **Lembke, A**., Humphreys, K. The Opioid Epidemic as a Watershed Moment for

Physician Training in Addiction Medicine, *Academic Psychiatry*, 2018.

56. Harrison, T. K., Kornfeld, H., Aggarwal, A. K., & **Lembke, A.** Perioperative Considerations for the Patient with Opioid Use Disorder on Buprenorphine, Methadone, or Naltrexone Maintenance Therapy. *Anesthesiology Clinics*, 2018; 36(3), 345–359. https://doi.org/10.1016/j.anclin.2018.04.002

Peer-Reviewed Online CME Courses

1. **Lembke, A**. *Prescription Drug Misuse and Addiction: Compassionate Care for a Complex Problem*: Enduring Online Course, Stanford Center for Continuing Medical Education, Stanford, California https://med.stanford.edu/cme/courses/online/rx-drug-misuse.html

2. **Lembke, A**. *Tapering Patients Off of Chronic Opioid Therapy*, Enduring Online Course, Stanford Center for Continuing Medical Education, Stanford, California, https://med.stanford.edu/cme/courses/online/opioid-taper.html

Book Chapters

1. Barry JJ, **Lembke A**, Huynh N: Affective Disorders in Epilepsy, in *Psychiatric Issues in Epilepsy: A Practical Guide to Diagnosis and Treatment*. Edited by Ettinger AB, Kanner AM. Philadelphia, Lippincott Williams and Wilkins, 2001, pp 45-72

2. Ketter T, Wang P, Dieckmann N, **Lembke A**, Becker O, Camilleri C: Brain Anatomic Circuits and the Pathophysiology of Affective Disorders, in *Brain Imaging in Affective Disorders*. Edited by Soares J. New York, Marcel Dekker, Inc., 2002, pp 79-118

3. Ketter T, Wang P, **Lembke A**, Sachs N: Physiological and Pharmacological Induction of Affect, in *The Handbook of Affective Science*. Edited by RJ D, KR S, HH G. New York, Oxford University Press, 2002, pp 930-962

4. Constantino MJ, **Lembke A**, Fischer C, Arnow BA: Adult Depression: Characteristics, Burdens, Models, and Interventions, in *Mental Disorders of the New Millenium, vol 1: Behavioral Issues*. Edited by Plante RG, Praeger Publishers, 2006, pp. 139-166

5. Barry JJ, **Lembke A**, Gisbert PA, Gilliam F. Affective Disorders in Epilepsy, in *Psychiatric Issues in Epilepsy*. Edited by Ettinger AB, Kanner AM. Philadelphia, Lippincott Williams & Wilkins, 2007, pp 203-247

6. **Lembke A**, DeBattista C. Review of a Randomized-Controlled Trial of Adjunctive Bupropion in the Treatment of SSRI-Induced Sexual Dysfunction, in *Progress in Neurotherapeutics and Neuropsychopharmacology*, vol 2. Edited by

Cummings JL, Cambridge University Press, 2007, pp 187-192

7. **Lembke, A**, Humphreys, K. Alcoholics Anonymous, in *Encyclopedia of Drugs, Alcohol & Addictive Behavior,* 3rd Edition. Edited by Korsmeyer P and Kranzler H, Macmillan Reference USA, 2008, pg. 122

8. Cohen, G., **Lembke, A**. Childhood Behavior and Later Substance Use, in *Encyclopedia of Drugs, Alcohol & Addictive Behavior*, 3rd Edition. Edited by Korsmeyer P and Kranzler H, Macmillan Reference USA, 2008

9. **Lembke A**, Humphreys K. Chapter 26: Substance Use Disorder Presenting as a Mood Disorder in *How To Practice Evidence Based Psychiatry: Basic Principles and Case Studies*. Edited by Taylor CB, APPI, Washington, D.C., 2009 , pp 233-246

10. **Lembke, A.,** Humphreys, K. Moos, R. Diagnosis, Development, and Treatment of Substance Use Disorders among Adolescents and Young Adults**,** in *Stanford School of Medicine Handbook of Developmental Psychiatry*. Edited by Steiner, H, NY, Jossey/Bass/Wiley, 2010, pp. 365-396

11. **Lembke, A**., & Humphreys, K. What self-help organizations tell us about the syndrome model of addiction. In Shaffer HJ (Editor-in-Chief), LaPlante DA and Nelson SA (Associate Editors), *APA Addiction Syndrome Handbook: Vol. 2. Recovery, Prevention, and other Issues*, Washington, DC: American Psychological Association, 2012, pp. 157–168

12. **Lembke, A**., Stanford, M. Clinical Management of Alcohol Use Disorders in the Neurology Clinic, Handbook of Clinical Neurology, Vol 125, 3rd Series, *Alcohol and the Nervous System* 1E, Edited by Sullivan, EV Pfefferbaum, A, Elsevier, 2014

13. Hall R, **Lembke A.** Substance Use Disorders in Adolescence. In: Steiner H (Ed) with Hall R. *Treating Adolescents* (2nd Edition). Westford, Massachusetts: Wiley, 2015, pp 141-164

14. **Lembke, A.,** Alcoholism and drug abuse, sociology of. In S. Martin (Ed.), *The SAGE encyclopedia of alcohol: Social, cultural, and historical perspectives*. (Vol. 1, pp. 98-104). Thousand Oaks, CA: SAGE Publications, Inc. 2015 doi: http://dx.doi.org/10.4135/9781483331096.n27

15. **Lembke, A.,** Moderation management. In S. Martin (Ed.), *The SAGE encyclopedia of alcohol: Social, cultural, and historical perspectives*. (Vol. 13, pp. 872-874). Thousand Oaks, CA: SAGE Publications, Inc. 2015 doi: http://dx.doi.org/10.4135/9781483331096.n334

16. **Lembke, A**., Humphreys, K. Self-Help Organizations for Substance Use Disorders, in *Oxford Handbook on Substance Use Disorders*, Edited by Sher, KJ, Oxford University Press, 2016

17. Ogbonna C, **Lembke A.** Alcohol and substance use and co-occurring behaviors. In Roberts LW (editor). University Student Mental Health: A Guide for Psychiatrist, Psychologists, and Leaders Serving in Higher Education. Arlington, VA: American Psychiatric Publishing, Inc., 2018.

18. **Lembke, A.,** Raheemullah, A. Addiction and Exercise. In Noordsy DL, (editor). Lifestyle Psychiatry: Using Exercise, Diet and Mindfulness to Manage Psychiatric Disorders. Washington DC: American Psychiatric Publishing. (In press)

Other Publications

1. **Lembke, A.** A Psychosocial Approach to Postpartum Depression *Psychiatric Times* 2002; XIX(6):11

2. **Lembke, A.** A downside of electronic health records: How 90 percent of Merced County, California patients became Albanian, *Scope*, the Stanford University School of Medicine blog, October 11, 2012.

3. **Lembke, A.** To reduce use, educate teens on the risks of marijuana and prescription drugs, *Scope*, the Stanford University School of Medicine blog, October 18, 2012.

4. **Lembke, A.** Why doctors prescribe opioids to patients they know are abusing them, *Scope*, the Stanford University School of Medicine blog, October 25, 2012.

5. **Lembke, A.** How to make alcoholics in recovery feel welcome this holiday season, *Scope*, the Stanford University School of Medicine blog, December 10, 2012.

6. **Lembke, A.** The DSM-V Gets it Right. *The Fix*, April 11, 2013.

7. **Lembke, A.** Inside the Mind of an Addiction Medicine Physician, *The Fix*, December 4, 2014.

8. **Lembke, A.** Unmet Expectations: Testifying before Congress on the Opioid Abuse Epidemic, *Scope*, the Stanford University School of Medicine blog, April 29, 2015

9. **Lembke, A.** Ask an Expert. Should I go off Suboxone? If so, how? *The Fix*, April 29, 2015

10. **Lembke, A**. Ask an Expert: Should I Go Through Detox if I'm Not Sure I Want to Be Abstinent? T*he Fix*, May 10, 2016

11. **Lembke, A.** Prince, opioids and the rest of us: America needs a massive public education campaign to help people hooked on Percocet and related drugs, *New York Daily News Op-Ed*, May 11, 2016

12. **Lembke, A.** Be sure the check the PDMP before prescribing controlled medications, *Psychiatric News*, June 17, 2016 http://psychnews.psychiatryonline.org/doi/full/10.1176/appi.pn.2016.pp6b2

13. **Lembke, A.** The Compassionate Doctor, the Narcissistic Injury, and the Prescription Opioid Epidemic. *The Fix*, Nov 30, 2016 https://www.thefix.com/compassionate-doctor-narcissistic-injury-and-prescription-opioid-epidemic

14. **Lembke, A.** Commentary provided in response to Joseph Bernstein's "Not the Last Word: Viscosupplementation, Opioid Overuse, and the Excesses of Empathy", *Clin Orthop Relat Res* (2017) 475:2369–2372

15. **Lembke, A.** Purdue Pharma is Done Promoting Opioids: Here's Why It's a Big Deal, *Fortune Magazine*, Feb 2018 http://fortune.com/2018/02/13/purdue-pharma-oxycontin-opioid-crisis/

16. **Lembke A.** Can medical marijuana replace opioids to relieve cancer pain? HemOnc Today. 2018;19(24):13.

Books

1. **Lembke, A.** *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*, Johns Hopkins University Press, November 15, 2016

Selected Invited Lectures/Testimony (last 5 years)

Regional Audience

1. Jan 2014 *The Overlooked Addict*, Psychiatry Grand Rounds, San Mateo County Health Systems Grand Rounds, San Mateo, CA

2. Mar 2014 *Patient, Providers, and Prescription Drug Abuse*, Dominican Santa Cruz Hospital CME Program and the Medical Education Speakers Network, Santa Cruz, CA

3. Mar 2014 *Prescription Drug Abuse: A Biopsychosocial Approach to a Complex Problem*, Psychiatry Grand Rounds, Alta Bates Summit Medical Center, Berkeley, CA

4. April 2014 *Prescription Drug Abuse: The Relapsed Addict*, Primary Care, San Mateo County Health Systems Grand Rounds, San Mateo, CA

5. Apr 2014 *The Opioid Epidemic: Pain and Prescription Drug Abuse*, Psychiatry Grand Rounds, Stanford University School of Medicine, Stanford, CA

6. July 2014 *The Intersection of Substance Abuse and Family Abuse*, Family Abuse Prevention Council, Stanford University School of Medicine, Stanford, CA

7. July 2014 *Prescription Drug Abuse and the Drug Seeking Patient*, Medicine Grand Rounds, Santa Clara Valley Medical Center, Santa Clara, CA

8. Sept 2014 *Buprenorphine as an Analgesic?* Addiction Services Grand Rounds, Santa Clara Valley Medical Center, Santa Clara, CA

9. Sept 2014 *Prescription Drug Abuse: A Prisoner's Dilemma*, Psychiatry CME Course, Kaiser Permanente Medical C enter, San Jose, CA

10. Nov 2014 *Pain, Addiction, and the Drug-Seeking Patient: Compassionate Care for a Complex Problem*, Inpatient CME Pain Course, Kaiser Permanente Medical Center, San Jose, CA

11. Feb 2015 *Drug Addiction and the Internet: Justin's Story*, Psychiatry Grand Rounds, Alta Bates Summit Medical Center, Berkeley, CA

12. Feb 2015 *Pain, Addiction, and the Drug-Seeking Patient: Compassionate Care for a Complex Problem*, Santa Clara Valley Medical Center CME Symposium on Addiction, Santa Clara, CA

13. Mar 2015 *The Prescription Drug Epidemic: Technology as Both Friend and Foe*, Northern California Psychiatric Society Annual CME Conference, Monterey, CA

14. Sept 2015 *The Prescription Drug Epidemic: Preserving Compassion for the Drug-Seeking Patient*, Mills Peninsula Health Services CME Lecture Series, San Mateo, CA

15. Oct 2015 *Addiction Medicine: Managing Prescription Drug Misuse and Addiction*, Emerging and Innovative Trends in Psychiatry and Behavioral Health, Stanford University School of Medicine, Stanford, CA

16. Oct 2015 *The Prescription Drug Epidemic: How Doctors are Complicit, and How We Can Do Better*, Regional Medical Center of San Jose CME Lecture Series, San Jose, CA

17. Dec 2015 *Exploring Dual Diagnosis: What came first, the substance use disorder or*

the psychiatric disorder, and does it even matter? Mills Peninsula Health Services CME Lecture Series, San Mateo, CA

18. Jan 2016 *The Prescription Drug Epidemic and the Doctor Patient Relationship,* San Francisco General Hospital Primary Care Grand Rounds, San Francisco, CA

19. Mar 2016 *Protecting our Developing Youth: Adolescent Addiction, Prevention and Recovery*, Keynote Speaker, Adolescent Counseling Services, East Palo Alto, CA

20. Mar 2016 *Opioid Therapy for Chronic Non-Cancer Pain*, 2016 Third Annual Addiction Medicine Conference, San Jose Valley Medical Center, San Jose, CA

21. Mar 2016 *The Prescription Drug Epidemic*, Keynote Speaker, Stanford Annual Adjunct Faculty Retreat, Palo Alto, CA

22. Sept 2016 *Pharmacotherapy for Substance Use Disorders*, Department of Psychiatry Annual CME Conference, Stanford University School of Medicine, Stanford, CA

23. Nov 2016 *Prescription Drug Misuse and the Doctor Patient Relationship*, Psychiatry, San Mateo County Health Systems Grand Rounds, San Mateo, CA

24. Mar 2017 *The Worst Opioid Epidemic in U.S. History: How did we get here, and how can we get out?* Santa Cruz Health Care Initiative, Santa Cruz, CA

25. Mar 2017 *The Canary in the Coal Mine: The Prescription Drug Epidemic as a Symptom of a Faltering Health Care System* Valley Care Medical, Pleasanton, CA

26. Mar 2017 *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop,* Northern California Psychiatric Society, Napa Valley, CA

27. Apr 2017 *Pharmacotherapy for Addictive Disorders,* Alta Bates Grand Rounds, Alta Bates Hospital Berkeley, CA

28. May 2017 *The Worst Opioid Epidemic in U.S. History: How did we get here, and how can we get out?* Stanford Health Matters, Stanford, CA

29. May 2017 *The Compassionate Doctor, the Suffering Patient, and the Prescription Drug Epidemic*, Central California Alliance for Health (the Alliance), Merced, California

30. May 2017 *The Compassionate Doctor, the Suffering Patient, and the Prescription Drug Epidemic*, Janus of Santa Cruz, Seaside, California

31. June 2017 *Overprescribing in the Elderly: Causes, Risks, and Interventions*, Keynote Speaker at the 17th Annual California Senior Injury Prevention Educational Forum, Oakland, CA

32. Feb 2018 *Is Marijuana a Harm Reduction Strategy?,* Stanford Psychiatry Grand Rounds, Stanford University School of Medicine, Stanford, CA

33. Mar 2018 *Raising T(w)eens in a Dopamine Saturated World*, Woodside Priory High School, Woodside, CA

34. Mar 2018 *Raising T(w)eens in a Dopamine Saturated World*, Sacred Heart High School, Menlo Park, CA

35. Apr 2018 *The Opioid Epidemic: What Doctors and Hospitals Can Do*, California Pacific Medical Center Internal Medicine Grand Rounds, San Francisco, CA

36. Apr 2018 *Adolescent Substance Abuse: Risk, Resilience, Prevention, and Treatment*, 2018 Adolescent Mental Wellness Conference, sponsored by Stanford University, Santa Clara, CA

37. Jul 2018 *Understanding the Opioid Crisis at the End of Life*, San Francisco Bay Area Hospice and Palliative Nurses Association, Stanford, CA

38. Aug 2018 *The Opioid Epidemic: How We Got Here, and How to Get Out,* Apple Corporation, Cupertino, CA

39. Oct 2018 *The Pleasure Pain Balance*, Los Altos High School "STEAM Week", Los Altos, CA

40. Jan 2019 *From Freud to Fentanyl: The Opioid Epidemic as a Symptom of a Faltering Health Care System*, Internal Medicine Grand Rounds, Santa Clara Valley Medical Center, Santa Clara, CA

41. Feb 2019 *Our Other Prescription Drug Problem (Benzodiazepines and How to Taper),* Internal Medicine Grand Rounds, San Mateo Medical Center, San Mateo, CA

National/International Audience

1. Sept 2014 *The Complex Patient: Pain, Mental Illness, and Addiction,* California Society of Addiction Medicine Annual Review Conference, Anaheim, CA

2. Sept 2015 *The Prescription Drug Epidemic: Compassionate Care for a Complex Problem,* Psychiatry Grand Rounds Speaker, Oregon Health Sciences University, Portland, CA

3. Oct 2015 *Chronic Pain and Addiction: The Compassionate Doctor, The Narcissistic Injury, and the Primitive Defense*, California Society of Addiction Medicine, State of the Art Annual Conference, San Francisco, CA

4. Oct 2015 *Prescription Drug Misuse and the Doctor Patient Relationship*, Keynote Speaker, American Correctional Healthcare Services Association, Tailoring Health Care for Inmates, Sacramento, CA

5. Mar 2016 *Chronic Opioids: Shifting the Paradigm*, Keynote Speaker, Samaritan Center & Health Career and Training Center, Lebanon, OR

6. Jun 2016 *The Compassionate Doctor, the Drug Seeking Patient, the Narcissistic Injury, and the Primitive Defense*, Keynote Speaker, Cedar Sinai Annual Psychiatric Conference, Los Angeles, CA

7. Sept 2016 *Myths and Facts about Opioids*, DCRx: The DC Center for Rational Prescribing; http://doh.dc.gov/dcrx, Washington, DC

8. Sept 2016 *Getting Patients Off of Opioids*, DCRx: The DC Center for Rational Prescribing; http://doh.dc.gov/dcrx, Washington, DC

9. Oct 2016 *State of the Art Treatment for Substance Use Disorders and other Addictions*, Keynote Speaker, 3-part lecture series, Beijing University, #6 Hospital, Beijing, China

10. Jan 2017 *Effective Strategies for the Non-Adherent Buprenorphine Patient: Rational Monitoring and Contingency*, California Society of Addiction Medicine, Treating Addiction in the Primary Care Safety Net, Webinar

11. Feb 2017 *How to safely taper patients off high dose prescription opioids for chronic pain*, Keynote Speaker, California Center for Care Innovations, Treating Addiction in the Primary Care Safety Net, Los Angeles, CA

12. Feb 2017 *The Worst Opioid Epidemic in U.S. History: How did we get here, and how can we get out?* Stanford Parents Weekend Back to School, Stanford, CA

13. Feb 2017 *When Pain Treatment Becomes Addiction Treatment*, American Psychological Association Annual Meeting, San Francisco, CA

14. Feb 2017 *Parallel Crises: The Over and Under Prescription of Opioids*, American Association of Medical Colleges (AAMC) Webinar

15. Mar 2017 *How Doctors Contributed to the Opioid Epidemic, and What We Can Do to Fix It*, Intermountain Health Care Book Club Speaker for *Drug Dealer, MD*, Intermountain Health Care, Salt Lake City, UT

16. Mar 2017 *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*, Culture and Politics of Mental Health, Anthropology 1737-1020, Professor Tomas Matza, University of Pittsburg, Pittsburg, PA

17. Apr 2017 *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop,* Stanford TEDx, Stanford, CA

18. Apr 2017 Invited speaker, 6th Annual Health Technology Forum Innovation Conference: Common Good! Stanford University School of Medicine, Stanford, CA

19. Apr 2017 *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop,* Keynote Speaker, 8th Annual Lloyda C. Elam Symposium, Meharry Medical College, Nashville, TN

20. Apr 2017 *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop,* Keynote Speaker, Association of Contextual Behavioral Sciences (ACBS), Chicago, IL

21. May 2017 *Invisible Forces Driving the Opioid Epidemic: From Disability Reform to Illness Narratives,* Keynote Speaker, OPG 6th Annual Pain Conference Agenda, Ashland, OR

22. May 2017 *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop,* Internal Medicine Residency Program Invited Visiting Professor and Grand Rounds Speaker, Johns Hopkins Bayview Medical Center, Baltimore, MD

23. June 2017 *Invisible Forces Driving the Opioid Epidemic: From Disability Reform to Illness Narratives,* Keynote Speaker, PharmedOut Annual Conference, Georgetown University Medical Center, Washington, DC

24. Sept 2017 *The Opioid Epidemic*, Keynote Speaker, Department of Labor West Coast Symposium, San Francisco, CA

25. Sept 2017 *Treating Addiction without Feeding It*, Keynote Speaker, American Correctional Health Services Association (ACHSA) "Modern Challenges in Jails and Prisons", San Jose, CA

26. Sept 2017 *Invisible Forces Driving the Prescription Drug Epidemic: From Disability Reform to Illness Narratives,* Keynote Speaker, The International Benzodiazepine Symposium, Redmond, OR

27. Sept 2017 *Reframing Medical Practice Involving Controlled Substances*, Keynote Speaker, The Association of State and Territorial Health Officials (ASTHO) 2017 Annual Conference, Washington, DC

28. Oct 2017 *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop,* Keynote Speaker, The Patient Safety Institute for Mission Health 3rd Annual National Patient Safety Conference – Cultivating a Culture of Safety, Asheville, NC

29. Nov 2017 *The Opioid Epidemic, How We Got Here, and How We Can Get Out*, Keynote Speaker, American Association of Medical Colleges, Learn, Serve, Lead, Boston, MA

30. Nov 2017 *The Opioid Fallout: Lives, Jobs and a Lost Generation*, Bloomberg News Live, The Year Ahead, Bloomberg Headquarters, New York City, NY

31. Nov 2017 *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*, Grand Rounds Speaker, Westchester Medical Center, Westchester, NY

32. Dec 2017 *The Opioid Epidemic: How We Got Here, and How We Can Get Out*, Keynote Speaker, Primary Care and Behavioral Health Integration Summit, Health Quality Partners, San Diego, CA

33. Jan 2018 *How to Survive in a Dopamine Saturated World*, Psychiatry Grand Rounds, Vanderbilt University School of Medicine, Nashville, TN

34. April 2018 *Drug Dealer, MD*, Keynote Speaker, STAR Trauma Recovery Center, Ohio State University Medical School, Columbus, OH

35. May 2018 *The Opioid Epidemic: What Doctors and Hospitals Can Do*, Alpha Omega Alpha Visiting Professorship, Psychiatry Grand Rounds, University of Kansas School of Medicine, Kansas City, KS

36. May 2018 *Opioids, Pain and Addiction Treatment: Pioneering Change*, Oregon Pain Guidance Annual Conference, Eugene, OR

37. June 2018 *The Opioid Epidemic, How We Got Here and How to Get Out*, Indiana Prosecuting Attorneys Council (IPAC), invited speaker, , French Lick, IN

38. June 2018 *What is Addiction and How to Treat It*, Perrin's Opioid Litigation Conference, Dallas, TX

39. Aug 2018 Moderator, *Beyond Nature and Nurture – Social Determinants of Addiction and Health*, California Society of Addiction Medicine State of the Art Annual Conference, San Francisco, CA

40. Aug 2018 *Drug Dealer, MD: The Opioid Crisis*, Apple Corporation Wellness Outreach, Cupertino, CA

41. Sept. 2018 *The Opioid Epidemic: How We Got Here, and How to Get Out*, Public Funds Forum, Laguna Beach, CA

42. Sept 2018 *Drug Dealer, MD: The Opioid Crisis*, Baton Rouge Health District

Community Service Talk and Medical Center Grand Rounds, Baton Rouge, LA

43. Sept 2018 *Drug Dealer, MD: The Opioid Crisis*, Montrose Annual CME Conference, Montrose, CO

44. Oct 2018 *The Opioid Epidemic: From Freud to Fentanyl*, Keynote Speaker, PerformRX Pharmacy Benefits Manager Annual Conference, Orlando, FL

45. Oct 2018 *The Opioid Epidemic: How We Got Here, Where We Are Now, and How to Get Out*, Keynote Speaker, Distinguished Lecture Series, Annual Meeting of the American Academy of Psychiatry and the Law (AAPL), Austin, TX

46. Oct 2018 *Drug Dealer MD: The Opioid Epidemic*, Keynote Speaker, Psych Congress, Orlando, FL

47. Nov 2018 *The Opioid Epidemic: The View From Inside Medicine*, The Baldwin Seminar Distinguished Lecture Series, the ACGME, Chicago, IL

48. Dec 2018 *The Opioid Epidemic: From Freud to Fentanyl*, Tector Lecture: 69th Annual Refresher Course for Family Physicians, Montreal, Canada

49. Dec 2018 *How to Taper Patients Off of Chronic Opioid Therapy*: 69th Annual Refresher Course for Family Physicians, Montreal, Canada

50. Feb 2019 *The Opioid Epidemic: How We Got Here, Where We Are Now, and How to Get Out*, National Keynote Speaker, Ohio State University Inter-Professional Summit, Columbus, Ohio

51. Feb 2019 *The Opioid Epidemic: How We Got Here, Where We Are Now, and How to Get Out*, Keynote Speaker, Pain and Addiction Summit, AT&T Conference Center/University of Texas, Austin, TX

United States Government Testimony/White House Appearances/Consulting

1. Apr 2015 Expert testimony for the Congress of the United States, House of Representatives, Committee on Energy and Commerce, Subcommittee on Oversight and Investigations hearing entitled "Combatting the Opioid Abuse Epidemic: Professional and Academic Perspectives," Washington, D.C. https://democrats-energycommerce.house.gov/committee-activity/hearings/hearing-on-combatting-the-opioid-abuse-epidemic-professional-and

2. Sept 2015 Expert testimony for the White House Symposium, "Medicine Responds to the Need for Addiction Expertise", The Office of National Drug Control Policy, The White House, Washington, D.C. https://obamawhitehouse.archives.gov/the-press-office/2015/09/18/white-house-drug-policy-office-hosts-%E2%80%9Cmedicine-responds-addiction%E2%80%9D

3. Sept 2016 Expert testimony for the United States Senate, Committee of Homeland Security and Government Affairs, Permanent Subcommittee on Investigations, on the overuse and overprescribing of prescription opioids, "Combatting the Opioid Epidemic: A Review of Anti-Abuse Efforts by Federal Authorities and Private Insurers", Washington, D.C.

4. Oct 2016 Expert testimony for the White House Symposium, "Academic Medical Centers as Centers of Excellence in Addiction Medicine", The Office of National Drug Control Policy, The White House, Washington, D.C. http://www.abms.org/news-events/white-house-symposium-briefing-session-on-addiction/

5. May 2017 Provided consultation on curbing the opioid epidemic to Nevada's Office of the Governor

6. May 2017 Provided consultation on curbing the opioid epidemic to Kentucky's Office of the Governor

7. Sept 2017 Expert Spoken and Written Testimony for the Congress of the United States, House of Representatives, "Addiction Medicine: The Urgent Need for Trained Physicians", hosted by The Addiction Medicine Foundation and co-sponsored by the Congressional Prescription Drug Abuse Caucus, the Congressional Addiction Treatment and Recovery Caucus, and the Congressional Bipartisan Heroin Task Forcehttps://www.youtube.com/watch?v=y6kBoQckmHw

8. Jan 2018 Expert testimony in federal court, Judge Dan Polster presiding, in the multi-district litigation lawsuit against opioid manufacturers and distributors https://www.law360.com/articles/1008010/inside-the-opioid-mdl-s-big-closed-door-hearing

9. March 20, 2019 Testimony by Stanford University Professor Anna Lembke to Joint Hearing of Senate and General Assembly Health and Human Services Committees on "Opioids, cannabis, and vaping: Using science to protect public health" State of Rhode Island

Media Appearances (last 5 years)

1. Apr 2015 *Public Radio International-To the Point*, hosted by Warren Olney, prescription opioid and heroin abuse in America, invited expert.

2. Oct 2015 *OnPoint, National Public Radio*, the prescription opioid epidemic, invited expert

3. Mar 2016 *Al Jazeera* live programming, the new CDC guidelines on opioid prescribing, invited expert

4. Mar 2016 *KCBS Radio*, San Francisco, the new CDC guidelines on opioid prescribing, invited expert

5. Apr 2016 *The Today Show* on NBC, NY, New York, appearance with Mehmet Oz discussing "The Opioid Epidemic"

6. May 2016 *KCBS Radio*, San Francisco, the FDA approves Probuphine, a buprenorphine implant, invited expert

7. Oct 2016 *Opioids: Last Week Tonight with John Oliver* (HBO), https://www.youtube.com/watch?v=5pdPrQFjo2o

8. Nov 2016 *Sirius XM Radio*, invited guest to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*

9. Nov 2016 *Wisconsin Public Radio's "Central Time" Show*, invited guest to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop* *http://www.wpr.org/connection-between-illicit-drugs-and-doctors*

10. Nov 2016 *The Healthcare Policy Podcast with David Introcaso*, invited podcast to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop* http://www.stitcher.com/podcast/david-introcaso-2/the-healthcare-policy-podcast/e/what-explains-the-opioid-epidemic-dr-anna-lembke-discusses-48277528

11. Nov 2016 *Straight Talk MD with Frank Sweeny* invited podcast to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop* http://straighttalkmd.com/podcast/drug-dealer-md-opioid-epidemic-anna-lembke-md/

12. Nov 2016 *Conversation on Healthcare Reach MD Radio*, invited guest to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop* *http://www.chcradio.com/episode.php?id=360*

13. Nov 2016 *KALW Local Public Radio*, invited guest to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop* *http://kalw.org/post/city-visions-how-doctors-fueled-opioid-epidemic#stream/0*

14. Nov 2016 *Forum with Michael Krasny (KQED-FM)* invited panelist to discuss "The Surgeon General's Report: Facing Addiction in America," https://ww2.kqed.org/forum/2016/11/28/addiction-is-illness-not-a-moral-failing-says-surgeon-general/

15. Nov 2016 *Stanford Scope 1:2:1 Podcast with Paul Costello* invited podcast to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why*

It's So Hard to Stop http://med.stanford.edu/news/all-news/one-to-one/2016/drug-dealer--md--how-physicians-are-fueling-the-opioid-epidemic.html

16. Dec 2016 *Straight Talk MD with Frank Sweeny* invited podcast to discuss "The Surgeon General's Report: Facing Addiction in America," https://www.acast.com/straighttalkmd/facing-addiction-in-america-the-surgeon-generals-report

17. Dec 2016, *NPR Fresh Air with Terry Gross* 'Drug Dealer, M.D.': Misunderstandings And Good Intentions Fueled Opioid Epidemic invited interview to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop* *http://www.npr.org/sections/health-shots/2016/12/15/505710073/drug-dealer-md-contends-that-well-meaning-docs-drove-the-opioid-epidemic*

18. Dec 2016 *The Jimmy Moore Show* invited podcast to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*

19. Feb 2017 *WILK Radio, The Sue Henry Show* invited guest to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*

20. Feb 2017 Reach, MD with host John J. Russell, MD invited guest to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop* https://www.reachmd.com/programs/book-club/drug-dealer-MD-how-doctors-duped-patients-hooked-why-so-hard-stop/8512/

21. Mar 2017 *MSNBC with Chris Hayes*, live guest appearance to discuss the opioid epidemic in West Virginia https://www.youtube.com/watch?v=0Ar30-kDSUQ&sns=em

22. Mar 2017 *Stanford Law School Wellness Project Podcast*, with Dr. Joseph Bankman and Dr. Sarah Weinstein, to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop* www.law.stanford.edu/wellnessproject

23. Mar 2017 *SiriusXM's Tell Me Everything with John Fugelsang,* invited guest to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*

24. June 2017 *The Texas Standard* Radio Show, invited guest to discuss the FDA decision to ask Endo Pharmaceuticals to withdraw Opana ER from the market http://www.texasstandard.org/stories/fda-wants-painkiller-favored-by-opioid-abusers-off-the-market/

25. June 2017 NBC *Television Sunday Night with Megyn Kelly*, invited expert to discuss marijuana legalization http://www.nbc.com/sunday-night-with-megyn-kelly/video/sunday-night-with-megyn-kelly/3536915

26. June 2017 *KCBS Radio in San Francisco* invited guest to discuss the ongoing opioid epidemic

27. July 2017 KPCC's AirTalk with host Larry Mantle, live guest appearance to discuss the opioid crisis http://www.scpr.org/programs/airtalk/2017/07/20/58084/in-the-context-of-the-opioid-crisis-doctors-discus/

28. July 2017 Jose Calderon Mindful Psychiatry Live Radio and Podcast, invited guest to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop* http://wholebodymentalhealth.libsyn.com/hard-pill-to-swallow-drug-dealer-md-with-dr-anna-lempke-md-7-5-17

29. Aug 2017 KQED Forum with Michael Krasny Live Radio Broadcast, invited guest to discuss *Rise in High-Risk Drinking a Public Health Crisis, New Study Finds*

30. Aug 2017 MSNBC with Chris Hayes, live guest appearance to discuss President Trumps inaction on the opioid epidemic http://www.msnbc.com/all-in/watch/donald-trump-has-done-nothing-on-the-opioid-crisis-1032009795986

31. Sept 2017 KPCC's AirTalk with host Larry Mantle, live guest appearance to discuss CVS Pharmacy's announcement it will limit opioid prescriptions to seven days for certain conditions for new patients seeking drugs for pain relief. http://www.scpr.org/programs/airtalk/2017/09/22/59288/how-much-would-cvs-s-7-day-limit-on-painkiller-pre/

32. Oct 2017 BBC Newshour on BBC World Service radio on the opioid epidemic with host James Menendez http://www.bbc.co.uk/programmes/w172vghc8jkrr3g

33. Oct 2017 NBCUniversal live in the studio with Dr. John Torres, One Nation Overdosed: Doctors Speak Out http://qlnk.io/ql/59f0f15be4b0945e5d8ff73f

34. Oct 2017 KPIX 5 CBS San Francisco Trump declares the opioid epidemic a public health emergency http://sanfrancisco.cbslocal.com/video/3752604-critics-say-trumps-opioid-announcement-doesnt-go-far-enough/

35. Oct 2017 KPIX 5 CBS San Francisco commentator on bay area parents using marijuana http://sanfrancisco.cbslocal.com/2017/11/04/marin-mom-marijuana-makes-her-better-parent/

36. Jan 2018 KQED with Brian Watt on "smartphone addiction" https://soundcloud.com/kqed/investors-urge-apple-to-take-action-to-curb-digital-device-overuse-among-children

37. Feb 2018 Sirius/XM radio with Clare Marie Gauthier, Co-Host, Dave Nemo Weekends, RadioNemo of North America, on the opioid epidemic and *Drug Dealer,*

MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop

38. Feb 2018 KQED News radio, report on Purdue Pharma's decision to stop marketing opioids directly to doctors

39. Feb 2018 NPR Smartphone Detox, How to Power Down in a Wired World https://www.npr.org/sections/health-shots/2018/02/12/584389201/smartphone-detox-how-to-power-down-in-a-wired-world

40. Mar 2018 Sirius/XM Radio with Clare Marie Gauthier, Co-Host, Dave Nemo Weekends, RadioNemo of North America, on addiction treatment

41. Mar 2018 Sirius/XM Radio "Doctor Radio", on the silent benzodiazepine epidemic

42. Mar 2018 Sirius XM Radio: POTUS Channel 124, "Steele & Ungar", on new Center for Medicare and Medicaid Services regulations to restrict opioid prescribing

43. Mar 2018 KPCC's AirTalk with host Larry Mantle, live guest appearance to discuss new Center for Medicare and Medicaid Services regulations to restrict opioid prescribing

44. Mar 2018 Science VS. with Rose Rimler, "Opioids: Kicking America's Addiction" https://www.gimletmedia.com/science-vs/opioids-kicking-americas-addiction#episode-player

45. April 2018 KQED Forum with Michael Krasny, Medical Community Divided On Medicare's Policy to Shorten High-Dose Opioid Prescriptions, live guest appearance, https://www.kqed.org/forum/2010101864587/medical-community-divided-on-medicares-policy-to-shorten-high-dose-opioid-prescriptions

46. May 2018 Radio Health Journal with Reed Pence: The Opioid Epidemic, http://mediatracks.com/shows/RHJ_18-17.mp3

47. May 2018 Straight Talk MD: Health | Medicine | Healthcare Policy | Health Education | Anesthesiology, The Cannabis Conversations: Part II with Anna Lembke MD http://straighttalkmd.com/podcast/the-cannabis-conversations-part-ii-with-anna-lembke-md/

48. June 2018 The Future of Everything with Russ Altman (Stanford Radio), 06/18/18. In a recent segment on Stanford Radio, **Russ Altman** discussed the rise of the opioid epidemic in the United States with **Anna Lembke**. https://soundcloud.com/user-458541487/facing-addiction-with-guest-anna-lembke

49. July 2018 NBC News with Dr. John Torres to discuss benzodiazepines https://www.nbcnews.com/nightly-news/video/is-anti-anxiety-medication-the-next-u-s-drug-crisis-1287215683720?cid=eml_onsite

50. October 2018, Featured in NOVA/PBS documentary ADDICTION, Produced, Directed and Written by Sarah Holt, Co-producer Julie Crawford http://www.holtproductions.org; http://www.pbs.org/wgbh/nova/body/addiction.html

51. March 11, 2019 Features on Spectrum News In Focus, What's Causing the Opioid Crisis, with Renee Eng, https://spectruminfocus.com/section/in-focus/in-focus/2019/03/11/in-focus--what-s-causing-the-opioid-crisis#

Anna Lembke, M.D. Report

EXHIBIT B

List of Materials Considered

EXHIBIT B

MATERIALS CONSIDERED

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Anna Lembke, M.D. Report

EXHIBIT C

Statement of Compensation Rate

Anna Lembke, M.D.
Stanford University School of Medicine
Department of Psychiatry and Behavioral Sciences

Expert Witness Fee Schedule: *Opioid MDL 2804*

Work	Details	Fee
Preliminary Work	Telephone conferences, record review, report writing, and travel	$500 per hour
Court Work	Court appearances and depositions	$800 per hour
Expenses	Travel and other reasonable out-of-pocket expenses	Reimbursement

Expert fees and expenses are not contingent on the outcome of any case pursued by: **Opioid MDL Counsel.**

Anna Lembke, M.D. Report

EXHIBIT D

Prior Testimony

Anna Lembke, M.D.
Stanford University School of Medicine
Department of Psychiatry and Behavioral Sciences

Prior Testimony

1. People v. Ingram, Philip Morris (Sup. Ct. of CA, Docket 62-144622)